OXIDATIVE HECK REACTIONS WITH TERMINAL OLEFINS

BY

JARED H. DELCAMP

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2010

Urbana, Illinois

Doctoral Committee:

Associate Professor M. Christina White
Professor Scott E. Denmark
Associate Professor Paul J. Hergenrother
Professor John A. Rogers

ABSTRACT

Sequential transformations in a single reaction have the potential to dramatically increase efficiency with respect to resources, time, and number of steps to access key intermediates. When sequential C-H bonds are activated a bifunctional handle arises from seemingly inert functionality. This work describes a one-pot sequential allylic C-H esterification, vinylic C-H arylation. A previously reported Pd(II)/sulfoxide system is used to generate branched allylic esters from α-olefins with only the addition of an aryl boronic acid to the reaction mixture. Styrenyl allylic esters are generated in good overall yield and excellent selectivities. The wide functional group tolerance and mild conditions of this three-component coupling reaction provide an attractive manifold for the rapid build-up of dense functionality around terminal olefins with minimal protecting group strategies or undesirable oxidation/reduction reactions. The synthetic utility of this reaction has been demonstrated through the synthesis of several intermediates to biologically active molecules.

The ready availability and inertness of α-olefins relative to the oxidized precursors required for other C—C bond forming methods means that fewer steps are required for their installation and maintenance throughout a synthetic sequence. Previously, allylic esters served as non-resonance directing groups on terminal olefin for the vinylic C—H arylation (Heck reaction). This manifold is unique because previous intermolecular Heck reaction conditions require an excess of resonance activated olefin coupling partner. Further exploration of directing groups to determine the underlying directing factors led to the discovery of several terminal olefin classes with diverse

directing elements. A general and highly selective intermolecular Heck arylation of non-resonance stabilized α-olefins with aryl and stryenyl boronic reagents has been developed. The Pd(II)/sulfoxide catalyzed Heck reaction is performed under oxidative, acidic conditions and proceeds with good yields and excellent regio- and stereoselectivities to generate linear *E*-arylated olefins.

Polyenes are prevalent motiefs in natural products and pharmaceuticals. Polyene functionality often requires mild and selective synthetic methods. The Heck vinylation uses orthogonally reactive C-H bonds and these bonds are often easy to carry through synthetic sequences. Despite this advantage, the synthetic potential of the intermolecular Heck reaction has not been realized in complex molecule formation. A method has been developed which overcomes the previous intermolecular Heck-vinylation shortcomings of excess terminal olefin and required resonance activation for regio- and stereoselectivities. The Pd(II)/sulfoxide catalyzed oxidative Heck vinylation proceeds under mild conditions to give polyene products with a variety of substitution patterns amid diverse functionality. The polyenes are formed in synthetically relevant yields with excellent stereoselectivities. Overall, the oxidative Heck vinylation compares favorably with many of the methods commonly used to synthesize polyunsaturated hydrocarbon segments. This method increases the synthetic potential of the intermolecular Heck reaction closer to that of other classic palladium cross-couplings.

ACKNOWLEDGMENTS

I would like to thank Professor M. Christina White for excellent guidance with regard to which problems to attack, persistence in aiding my development as a writer, and for understanding some insanity properly directed can be useful. I have learned countless lessons about becoming an advisor vastly ranging from the importance of recruiting quality people which will one day be called colleagues to the importance of how to use criticism to its fullest to become better. I will certainly miss her unabated passion for solving problems as evidence through belt buckles, tattoos, and work ethic. I have appreciated her big picture analysis of methods developed in and out of this lab and it was this attitude which originally attracted me to this lab. I will undoubtedly take this attitude that fosters courage to attack global problems by asking the correct (often risky) questions to any future areas of research.

I would like to thank Professor John Anthony for all his guidance beginning with my sophomore year at the University of Kentucky through the present. I was intensely fortunate to have observed his passion for science and listened to his encouragement to stop the medical school route and pursue research. I was even more fortunate to have the opportunity to work on a very successful project from the start. It was that intoxicating success which began my addiction of discovery. He has continued to grant me excellent advice from the beginning and has set a standard for the type of attitude I want to maintain especially toward confused pre-med students.

Professor Scott Denmark has set an excellent example of what it really means to love the literature. As a first year student at Illinois I felt as though literature was too vast to ever gain a confident handle on. After several years of Professor Denmark serving on

my committee and my attendance to his synthesis course, I have realized truly loving a field can grant you the dedication and commitment to know a significant amount of what has happened and is in progress in a field. I am thankful to graduate soon feeling tremendously less overwhelmed but still understanding how vast our scientific literature is.

I was granted the blessing of working with both Alex Brucks and Nicolaas Vermeulen on projects. Alex was brave enough to accept guidance from me and is the first student I directly mentored. She was undeniably a large asset to my second major project. At the time of agreeing to help develop her experimental techniques I viewed the time commitment as a real gamble; however, I can say the gamble was well placed. The time investment certainly 'paid' for itself; however, I unknowingly gained the opportunity to guide a very gifted student and the rewards of that are hard to measure. While working with Nic I learned the real potential of working with a colleague to achieve a similar goal. The speed of results gathered was astonishing given I had typically worked alone experimentally.

I appreciated the opportunity to both learn from and help create the laboratory techniques and philosophies entitled 'gorilla' chemistry from a crazed and now doctor Mark Chen. Aside from developing less than orthodox procedures, we have had the opportunity to share in the concept of 'relative pain' which not only served to make each of us stronger at the task at hand, but also made difficult tasks both competitive and comical. I both respect and fear what science is gaining in Mark Chen.

I admire Dustin Covell for maintaining some level of grasp on reality as Mark and I attempted to spiral toward lawlessness. He has been a good friend and has maintained

an inspiring level of rigorous experimentation no matter what the consequences. His passion is solid. I also suspect he is the 'minion' whereas he introduced me to competitive Halo which undoubtedly added at least 6 months to my Ph.D. Thanks?

Nicholaas Vermuelen and John Whitteck have both been good friends since the beginning of graduate school. I am thankful for their unique senses of humor and the stabilizing affects each of them have had throughout my graduate school experience. Our many hours of games and drinking have helped me with the play hard portion of my week.

I am grateful to have had the opportunity to work beside an incredible group of chemists. I have no doubts great future research will come from: Ken Fraunhoffer, Mark Chen, Dustin Covell, Nicholaas Vermeulen, Erik Stang, Sean Read, Grant Rice, Andrew Young, Alex Brucks, Marinus Bigi, Paul Gormisky, Shauna Paradine, and Iulia Strambeanu. I also have no doubts Mark Chen, Alex Brucks, Paul Gormisky, and Shauna Paradine are socially prepared for a diverse array of scenarios as each was forced to closely interact with me by sharing a bay.

To Michael Birbiglia: I am in the future too now.

I would like to thank my father, David Delcamp, for teaching me how to 'build character' on the farm through what most would call intense manual labor. He also instilled a level of personal discipline in me that has certainly paid off. He has encouraged me to excel in school and to make sure I had some fun too along the way. He is an inspiration in many ways.

Last, and undeniably most, I owe a tremendous thanks to my wife Leah Delcamp for a level of understanding and encouragement I could not have dreamed possible from

someone outside the field. She has seen, heard, and shared every last bit of frustration and success I have experienced in graduate school and been nothing but supportive the entire way. I owe her, Mac, Marley, and Monty my sanity. She not only entertains my ridiculous antics but frequently expands upon them. Because of her continual promotion of creativity and encouragement I now realize the scientific problems solved thus far never stood a chance of remaining unsolved and future problems are already cowering in fear.

TABLE OF CONTENTS

CHAPTER 1

SEQUENTIAL HYDROCARBON FUNCTIONALIZATION: ALLYLIC C-H OXIDATION/VINYLIC C-H ARYLATION

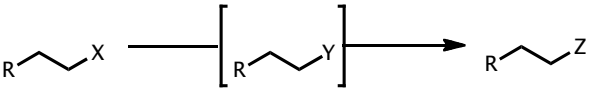
1.1 INTRODUCTION

Complex molecule synthetic strategies often rely heavily on the presence of heteroatom functionality that can be activated as nucleophiles via deprotonation or serve to make adjacent sites electrophilic centers. Carbanion synthetic strategies are prominent C-C bond forming methods employed during the construction of biologically active molecules which generally demonstrate high yields and great stereoselectivities.[1] Alternatively, transition metal based cross coupling reactions provide direct access to hydrocarbon frameworks without the requirement of adjacent heteroatom functionality for reactivity. However, both methods often rely on pre-activation of both coupling partners and this pre-activation often lengthens routes to important molecules due to (1) introducing the functionality and (2) adding additional steps to maintain functionality throughout a synthetic sequence. Ideally, C-H bonds could be used to both install the valuable heteroatom functionality commonly used in carbanion synthesis and as coupling partners for transition metal couplings (TMCs) to build carbon frameworks from inert functionality.

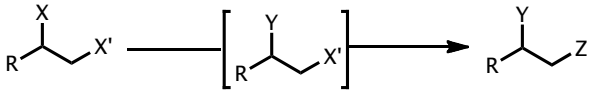
Sequential functionalizations performed in a single-pot enable the rapid build up of molecular complexity with minimal resources, time investment, and functional group manipulations.[2] Both linear and divergent sequential reactions have specific key advantages over standard single reaction sequences (figure 1). Linear sequential

Figure 1. One-pot sequential reactions

Linear Sequential Reactions



Divergent Sequential Reactions



reactions allow access to reactive intermediates without difficult isolation procedures. Divergent sequences enable the build up of molecular complexity at distinctly different sites generating compounds with two new functional handles in a single reaction pot.

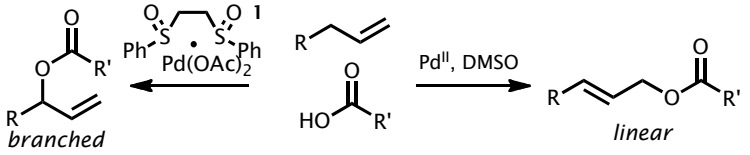
The development of mild, selective C-H activation reactions is gaining increasing attention.[3] C-H bonds are ubiquitous in pharmaceuticals and natural products and are commonly considered unreactive without adjacent oxygen or nitrogen functionality. Due to the inert nature of C-H bonds they can be carried through traditional synthetic sequences without the need for protecting groups or changes in oxidation state commonly needed for oxygen based strategies.[4] Foregoing these functional group manipulations (FGMs) can dramatically affect the number of synthetic steps and yield of the overall sequence.

Sequential one-pot functionalizations and C-H bond transformations both have the potential to dramatically streamline the synthesis of small molecules. Combining the two reaction pathways into a single reaction could greatly increase the rate of access to complex small molecules. When differentiable C-H bonds are transformed to distinctly different functionalities, a bifunctional handle arises from seemingly inert functionality. For maximal efficiency, a single catalyst capable of facilitating both C-H functionalization events may be selected if the desired reactions are paired properly. We

envisioned oxygenation of an allylic C-H bond followed by vinylic C-H bond activation via an oxidative Heck arylation with a single electrophilic palladium catalyst.

The White lab initially focused on the development of mild, selective C-H activation methods for the installation of allylic oxygen functionality with electrophilic palladium (II) catalysts (figure 2).[5] Based on catalyst choice either the branched or linear

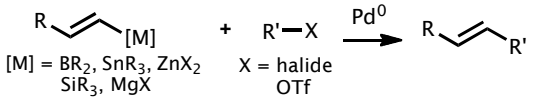
Figure 2. C-H bond oxygenation with electrophile Pd^{II} catalysts.



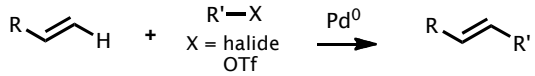
ester product could be selectively synthesized. Both catalysts are believed to generate highly electrophilic palladium intermediates as the active species which upon coordination to a terminal olefin weaken the allylic C—H bond to deprotonation. Importantly, the branched and linear products retain a now allylic functionalized olefin which is tremendously useful for further functionalizations.

Transition metal based cross-couplings often require prior activation of both coupling partners, typically via a carbon-metalated reagent and a halide or triflate. Unique among palladium-based TMCs is the Heck reaction which couples a vinylic C-H bond with either 1) a halide or triflate under reductive conditions or 2) a carbon-metalated intermediate under oxidative conditions to form C-C bonds (figure 3). Palladium (0)

Figure 3. Palladium Mediated Cross Couplings.
Suzuki, Stille, Negishi, Hiyama, Kumada Reactions

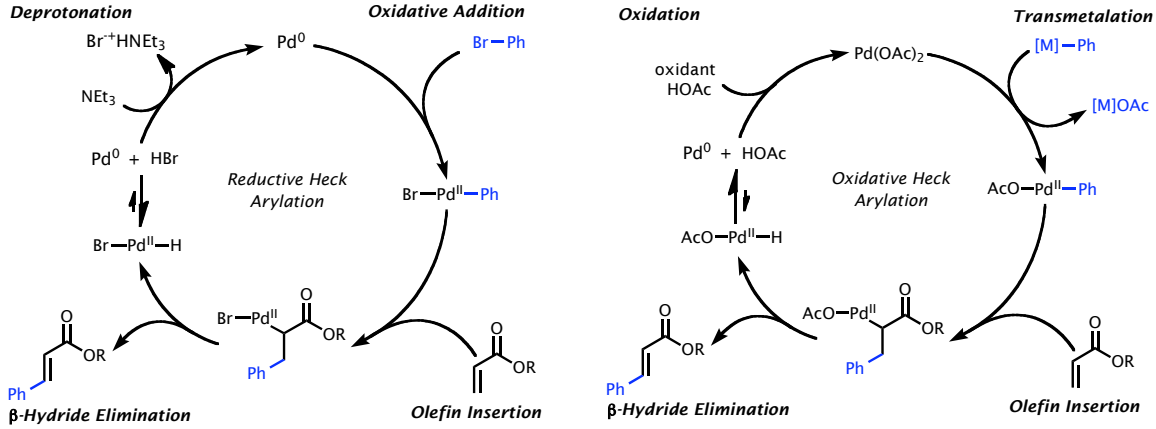


Heck Reaction



based reductive Heck couplings begin the catalytic cycle with an oxidative addition into either a halide or triflate, followed by olefin insertion, β-hydride elimination, and reductive elimination/deprotonation[6] to regenerate the palladium (0) catalyst (figure 4).

Figure 4. Comparison of Pd(0) vs Pd(II) catalytic cycles.



The oxidative palladium (II) based counterpart has a similar catalytic cycle with the exception of the palladium catalyst beginning with a transmetalation event and ending in a reoxidation. Importantly, the oxidative Heck reaction relies on an electrophilic palladium (II) source as opposed to the nucleophilic palladium (0) source in the reductive conditions to begin the catalytic cycle. A highly electrophilic palladium (II) catalyst is required for both the allylic esterification and the vinylic arylation. We envisioned sequential allylic, vinyl C-H bond transformations with a single catalyst by finding conditions suitable for both reaction to occur in a single pot.

We recognized several key challenges to performing an oxidative Heck arylation on branched allylic ester intermediates. The intermolecular Heck reaction is usually limited to resonance activated olefins for 1) increasing reactivity to olefin insertion and 2) controlling the regioselectivity for aryl insertion. Furthermore, olefins are typically not the limiting reagents for Heck arylations (3-5 equiv.) making the reactions impractical on valuable olefin starting materials. Significantly, electrophilic palladium (II) is known to

rapidly transmetalate arylsiloxane, aryltin, and arylboron reagents in the presence of base to promote transmetalation/catalyst regeneration.[7] Cationic palladium (II) complexes have been shown to be highly active catalysts for aryl boronic acid transmetalation and C=C bond insertions in conjugate additions reactions of aryl boronic acids to enones under neutral conditions.[8] However, the allylic C-H esterification is carried out under acidic reaction conditions and, to the best of our knowledge the transmetalation of boronic acids under these conditions has not been demonstrated. Providing these two significant challenges could be overcome, a novel sequential allylic C—H oxidation/vinylic C—H arylation would be possible using catalyst **1**.

We were able to develop a novel vinylic C—H arylation reaction on electronically unbiased olefins with aryl boronic acids that proceeds under mildly acidic, oxidative conditions. Importantly, the oxidative Heck arylation proceeds with the same palladium (II)/sulfoxide catalyst **1** as the branched allylic esterification with high regioselectivities and *E/Z* selectivities at mild temperatures (r.t.). This represents the first example of a palladium (II) mediated cross-coupling reaction with boronic acids under acidic, oxidative conditions.

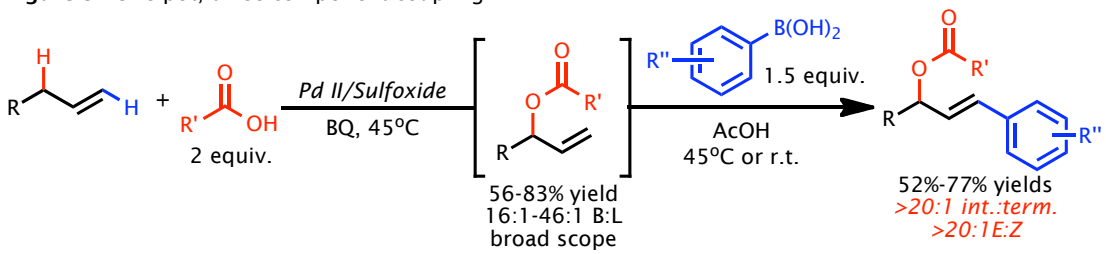
1.2 RESULTS AND DISCUSSION

1.2.1 Developing a Sequential Allylic C—H Oxidation/Vinylic C—H Arylation: Boronic Acid Scope

The development of this sequential allylic, vinylic C-H functionalization reaction began by simply adding 1.5 equivalents of phenyl boronic acid to the branched allylic oxidation reaction upon complete consumption of the terminal olefin starting material.

We were delighted to find that in the presence of carboxylic acids with no additional catalyst, the corresponding *E*-arylated allylic esters were generated in good yields with

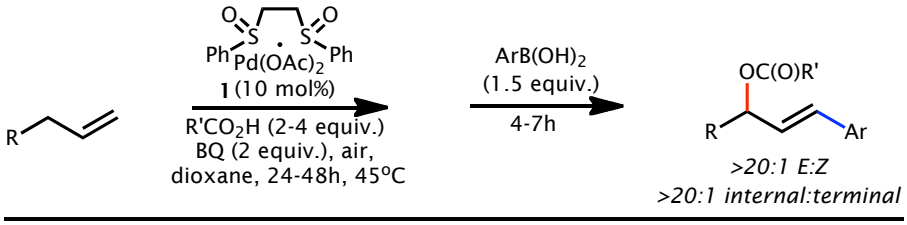
Figure 5. One-pot, three component coupling.

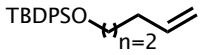
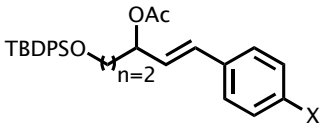
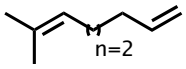
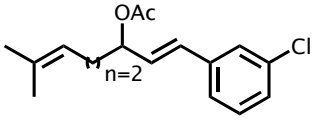
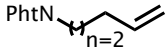
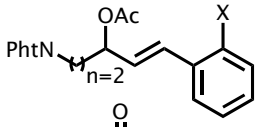
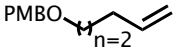
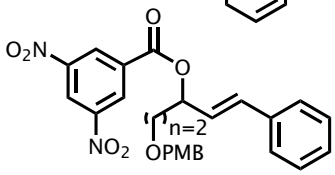
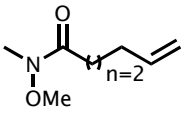
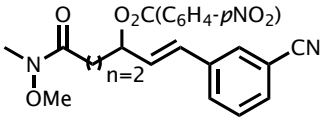
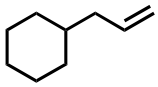
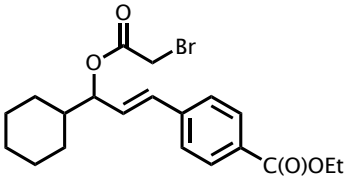
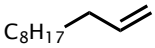
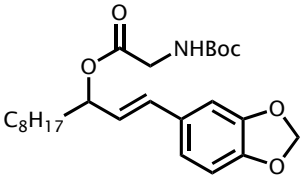


high stereo- and regio- selectivities (>20:1 *E:Z*, >20:1 internal:terminal olefin, figure 5). This one-pot, three component coupling reaction of α-olefins, carboxylic acids, and aryl boronic acids furnishes a wide range of *E*-arylated allylic esters in great selectivities and good yields (table 1).

We found 10 mol% palladium/bis-sulfoxide catalyst **1** effects sequential allylic C-H esterification/vinylic C-H arylation for a variety of α-olefins as well as electronically and sterically diverse carboxylic acids and boronic acids. The *E*-arylated allylic ester products were furnished in good yields as single isomers by crude ^{1}H NMR spectroscopy. Compounds **2-6** (table 1) demonstrate compatibility with both electron withdrawing and electron donating groups on the aryl boronic acids in this reactions. Significantly, electron rich boronic acids are known to undergo protodeboronation in acidic conditions; however, under these mild conditions preparatively useful yields of the desired products **3**, **9**, and **13** were isolated when the arylation was performed at room temperature.[9] As previously mentioned, oxidative Heck arylation conditions are typically basic which is often problematic for protodeboronation of electron withdrawn aryl boronic acids. However, under these novel acidic conditions electron deficient aryl boronic acids couple efficiently as seen for compounds **4-6** and **11-12**. Furthermore,

Table 1. Sequential three-component coupling reaction.



entry	olefin	product	isolated yield[a]
1 2 3 4 5			X: **2**, H = 74% **3**, OMe[b] = 52% **4**, Cl = 63%[c] **5**, F = 74% **6**,  = 60%
6			**7**, 63%[d]
7 8			X: **8**, Me = 73%[d,e] **9**, OMe = 55%[b,d]
9			**10**, 53%[d]
10			**11**, 77%[d]
11			**12**, 62%[c,d]
12			**13**, 69%[b]

[a]Average yields of isomerically pure material for two runs at 1.0 mmol. [b] Arylation performed at rt. [c] Arylation run for 24h. [d] BQ (1 equiv.), AcOH (1 equiv.) added for arylation when oxidation run >24h. [e]2.0 equiv. *o*-MePhB(OH)$_2$

extremely electron withdrawn 2-nitro, 4-nitro, 4-trifluoromethyl, and 3,5-di(trifluoromethyl) boronic acids all react smoothly in our system. *Ortho*-substituted aryl boronic acids are often problematic in coupling reactions due to both low reactivity and

deboronation pathways but they couple smoothly under these mild conditions (compounds **8** and **9**). Aryl halides are reactive through oxidative addition pathways under palladium (0) mediated reductive Heck conditions. The palladium (II) mediated oxidative conditions described herein do not react with aryl bromide and chloride functionalities (compounds **4**, **7**, and **15**), which establishes the complementarity of this oxidative reaction with standard palladium (0) based reductive reactions. Overall, dramatically few aryl boronic acids were found to be problematic in this system with the few notable exceptions being 1) aryl iodides because oxidative addition of the transient palladium (0) species to the C-I bond being competitive with benzoquinone reoxidation which leads to polymerizations, 2) significantly sterically encumbered aryl boronic acids (i.e. 2,6-dimethylaryl boronic acid), and 3) heteroaromatic boronic acids due to facile protodeboronation.

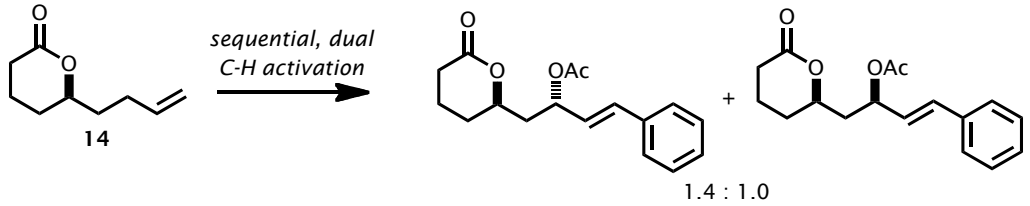
1.2.2 Developing a Sequential Allylic C—H Oxidation/Vinylic C—H Arylation: α-Olefin and Carboxylic Acid Scope

The scope of the α-olefin and carboxylic acid components were explored to demonstrate the utility of this three-component coupling. A wide range of polar functional group handles may be present including silyl and benzyl ethers, phthalimides and Weinreb amides (compounds **2**-**6** and **8**-**10**). Chemoselectivity was illustrated with the synthesis of compound **7** whereas the internal olefin remained unaffected throughout the sequential reaction. Although not required for reactivity, substitution proximal to the α-olefin is well tolerated as demonstrated when allylcyclohexane was used as a coupling partner (compound **12**). It is important to note the terminal olefin is the limiting reagent

in all cases which is dramatically different than previous intermolecular Heck reactions demanding 2-5 equivalents.

Interestingly, proximal functionality has little influence on the diastereoselectivity of the allylic C-H esterification reaction. When examining bis-homoallylic substituted α-olefins, only slight diastereoselectivity was observed for lactone substrate **14** (1.4:1 anti:syn, scheme 1). This result indicates the catalyst is not strongly influenced by adjacent functionality during the C-H esterification and offers a good opportunity for development of an asymmetric version capable of overriding inherent substrate bias.

Scheme 1. Inherent reaction bias is minimal for bishomoallylic substitution.

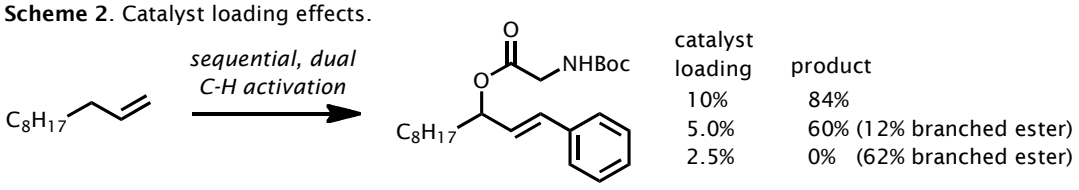


A diverse array of carboxylic acid coupling components were observed to give good reactivity. Both alkyl and aryl carboxylic acids readily couple with α-olefins and are tolerated during the Heck arylation. Once coupled, the allylic esters provide a functional handle for a number of reactions including several asymmetric reactions. Arylated 3,5-dinitrobenzoate and 2-bromoacetate allylic esters **10** and **12** may be further elaborated via asymmetric palladium (0) π-allyl substitution reactions and enolate-type Claisen rearrangements, respectively.[10] Esters such as arylated *p*-nitrobenzoate **11** which are readily hydrolyzed during basic workup affording the corresponding arylated allylic alcohols may be synthesized via this reaction manifold. Amino acid derivatives **13** and **15** were synthesized in good yields with only two equivalents of the carboxylic acid component. The three-component coupling reaction was found to proceed with higher yields with excess carboxylic acids. For valuable carboxylic acids, acetic acid may be

added after the allylic esterification has completed which allows for low loadings of complex acids.

Catalyst loadings were also explored in this reaction manifold. Lowering loadings below 10% is possible for some carboxylic acids (scheme 2). Catalyst loadings of 5% gave preparatively useful yields of the desired product but catalyst death became problematic whereas the yield is diminished in comparison to the 10% loading and significant amounts of non-arylated intermediate are observed. A loading of 2.5% gave only the non-arylated allylic ester in 62% yield with no desired product.

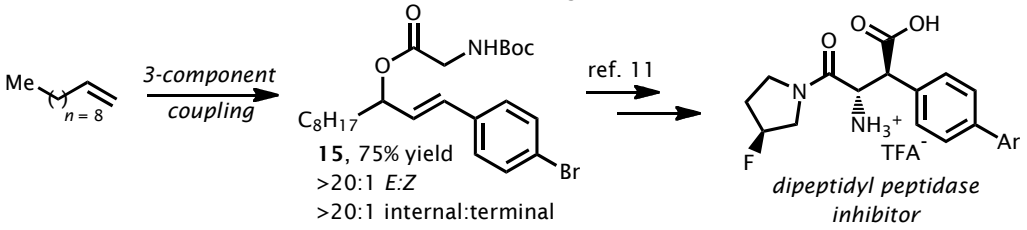
Scheme 2. Catalyst loading effects.



1.2.3 Synthetic Applications

A key benefit of this methodology is the ability to use inexpensive hydrocarbon starting materials to rapidly generate densely functionalized intermediates for complex molecule synthesis. Beginning with a hydrocarbon, a bifunctional handle is installed in a single step which is readily elaborated to medicinally important molecules. Pharmacologically relevant *E*-arylated allylic *N*-Boc glycine ester intermediates **13** and **15** were each synthesized in one-pot from a commercial hydrocarbon, an amino acid and an aryl boronic acids as single regio- and stereoisomers (>20:1 *E:Z*, >20:1 internal:terminal olefin, table 1 and scheme 3, respectively). Compound **15** serves as an intermediate which readily undergoes elaboration to a pharmaceutically important

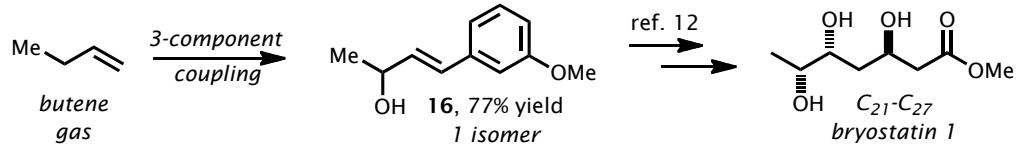
Scheme 3. Hydrocarbon to dense functionality in a single step.



dipeptidyl peptidase IV inhibitor via enolate-Claisen rearrangement of the amino ester to the γ,δ-unsaturated amino acid, Suzuki cross-coupling of the aryl bromide to a biaryl, and ozonolysis of the olefin to a carboxylic acid moiety.[11] This example nicely demonstrates the complementary nature of palladium (II) based catalytic cycles with palladium (0) based catalytic cycles, where as the aryl bromide would be difficult to preserve under palladium (0) reaction conditions.

Allylic alcohol **16** was synthesized in 77% yield directly from butene gas as limiting reagent (scheme 4). Significantly, improved yields of cinnamyl alcohol **16** were obtained when the reaction was run under an O_2 atmosphere (1 atm) instead of an air atmosphere which presumably aids in reoxidation of the palladium (II)/bis-sulfoxide catalyst **1**. The *E*-arylated allylic alcohol was further elaborated via enantioselective

Scheme 4. Butene gas conversion to a valuable synthetic intermediate in one step.

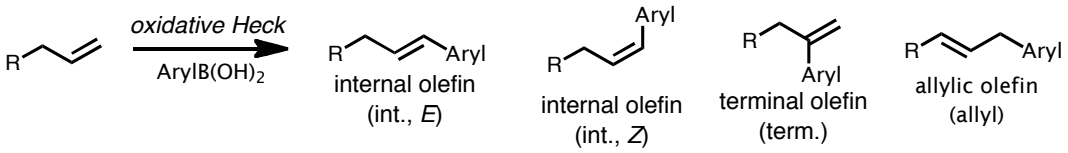


epoxidation resolution of the olefin and a Birch reduction, ozonolysis sequence of the *meta*-substituted anisol ring to form the *β*-ketoester in Evans synthesis of the C_{21}-C_{27} segment of bryostatin 1.[12] This series of selective reduction reactions can be used to convert molecules analogous to **16** to 1,3-diol subunits found in polyacetate-derived natural products.

1.2.4 The Oxidative Heck Reaction: Substrate Scope, Selectivities and Necessary Reaction Components

The selective vinylic C-H arylation step of the sequential reaction proceeds via an electrophilic palladium (II) promoted transmetalation and alkene bond insertion. A series of substrates were examined in the oxidative Heck arylation reaction to determine why this catalyst promotes vinylic C-H arylation in high regio- and stereoselectivities. The possible arylated product isomers are named based on the position/stereochemistry of the olefin (scheme 5). Allylic acetoxy and small alkoxy substituents undergo highly

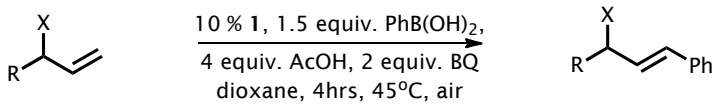
Scheme 5. Definitions of olefin selectivities in the oxidative Heck arylation.



siteselective vinylic C-H arylations to yield internal olefin products (table 2, entries 1-3). Substrates with small allylic alkyl substituents give a mixture of internal:terminal and internal:allylic olefin products significantly favoring the internal olefin isomer (table 2, entries 4 and 7). Large allylic substitution such as the allylic *gem*-dimethyl substituted substrate **25** or allylic OTBPDS substrate **21** gave excellent yields with great selectivities (table 2, entries 9 and 5). Consistent with a steric argument, a simple straight chain terminal alkene substrate **22** gave an inseparable mixture of internal, allylic, and terminal olefin isomers in low selectivity (4:1:1, table 2, entry 6). Finally, homoallylic benzyl (compound **24**) gave selectivities similar to those seen for small allylic alkyl substitutions indicating allylic ethers are much better substrates than homoallylic ethers (table 2, entry

8). The terminal olefin substrate scope and hypothesis about the origins of selectivities will be addressed more thoroughly in chapter 2.

Table 2. Substrate selectivities and scope of the oxidative Heck reaction.

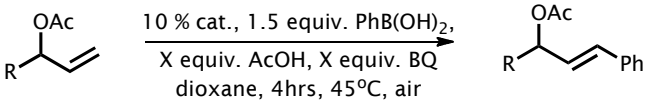


entry	substrate		isolated yield[a]	int.:term.[b]	int.:allyl[b]	*E*:*Z*[b]
1	X	X = OAc, **17**	98%	41:1[c]	>20:1	>20:1
2	alkyl	OMe, **18**	95%	>20:1	>20:1	>20:1
3		OBn, **19**	92%	>20:1	>20:1	>20:1
4		Me, **20**	75%	8:1	8:1	>20:1
5		OTBDPS, **21**	94%	>20:1	>20:1	>20:1
6		H, **22**	64%	4:1	1:1	>20:1
7	**23**		88%	8:1	8:1	>20:1
8	OBn O O **24**		97%	9:1	1:1	>20:1
9	**25**		100%	>20:1	---	>20:1

[a]Average yield for 2 runs done at 1.0 mmol. [b]Determined via ^{1}H NMR on crude reaction mixture unless noted. [c] Determined by GC analysis of crude material.

Since the newly developed oxidative Heck arylation had only been performed as part of a tandem sequence, experiments varying the components for the vinylic C-H arylation reaction were necessary to better understand the catalytic cycle. Catalyst **1**, carboxylic acid, and benzoquinone were all necessary for efficient vinylic C-H activation. Palladium acetate has been shown to undergo transmetalation with aryl boronic acids stoichiometrically in the absence of activators; however, the bis-sulfoxide ligand proved necessary under these conditions for efficient transmetalation of aryl boronic acids (37% vs 98% yields, table 3, entries 1 and 2). Consistent with a palladium (II) based catalytic cycle, benzoquinone was found to be necessary since only stoichiometric reactivity was

Table 3. Testing the importance of each component in the oxidative Heck-arylation.



entry	catalyst	AcOH	BQ	isolated yield[a]
1	**1**	4 equiv.	2 equiv.	98%
2	$Pd(OAc)_2$	4 equiv.	2 equiv.	37%
3	**1**	4 equiv.	---	8%
4	**1**	---	2 equiv.	71%
5	**1**	1 equiv.	2 equiv.	94%

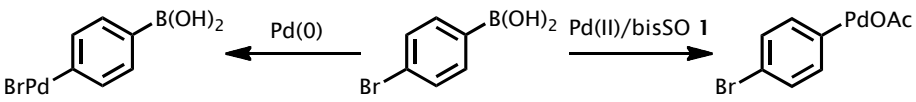
[a] Average yields for 2 rungs at 1.0 mmol.

observed in the absence of an oxidant (table 3, entry 3). Increased reactivity was observed in the presence of excess carboxylic acid and removal of the acid gave diminished and variable yields (71-24% yield, table 3, entries 1, 4, and 5). The diminished yield is likely due to carboxylic acid being necessary to regenerate the palladium carboxylate catalyst during reoxidation with benzoquinone (2 HX + Pd(0) + BQ → DHQ + PdX_2).

1.3 CONCLUSIONS

A novel one-pot three component coupling has been developed which converts α-olefin hydrocarbons, carboxylic acids, and arylboronic esters to *E*-arylated allylic esters with high regio- and *E:Z* selectivities. Densely functionalized building blocks are constructed from robust C-H bonds in a single step making this method suitable for high-throughput applications. A new reaction manifold has been explored using a palladium/bis-sulfoxide catalyst **1** to effect Heck-arylation of terminal olefins baring allylic oxygenates with arylboronic acids. This reaction manifold is complementary to

Scheme 6. Complementary reactivity of palladium (0) vs palladium (II).

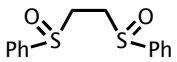


the standard basic, reductive manifold for generating palladium-aryl intermediates for cross-coupling reactions (scheme 6).

1.4 EXPERIMENTAL SECTION

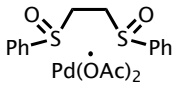
General Information: All commercially obtained reagents for the allylic oxidation, Heck arylation reaction were used as received: 1,4-benzoquinone (Sigma-Aldrich); 2-methoxyphenylboronic acid, 4-methoxyphenylboronic acid, 4-chlorophenylboronic acid, 4-fluorophenylboronic acid, 4-formylphenylboronic acid, 3-chlorophenylboronic acid, *o*-tolylboronic acid, 2-methoxyphenyl boronic acid, 3-cyanophenylboronic acid, and 4-methoxycarbonylphenylbornic acid (Frontier Scientific); phenylboronic acid (Sigma-Aldrich); $Pd(OAc)_2$ (Strem Chemicals). $Pd(OAc)_2$ was stored in a glove box under an argon atmosphere and weighed out in the air prior to use. Bottles of $Pd(OAc)_2$ that were found to give suboptimal yields for the Heck arylation were recrystalized according to the procedure provided below. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N,N-dimethylformamide (DMF) (Sure Seal) was obtained from Sigma-Aldrich and used as received. All allylic oxidation, Heck arylation reactions were run under air with no precautions taken to exclude moisture. An exception to this is the 1-butene reaction run under an atmosphere of O_2. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate staining. Flash column chromatography was

performed as described by Still et al.[13] using EM reagent silica gel 60 (230-240 mesh). ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). Regioselectivity of the Heck addition was determined by GC analysis with authentic terminal olefin standard. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.



1,2-bis(phenylsulfinyl)ethane: A 50 mL round bottomed flask (RBF) was charged with a stir bar, 2 g (7.19 mmol, 1 equiv.) of 1,2-bis(phenylthio)ethane, and 12.2 mL of acetic acid. A solution of H_2O_2 (50 wt%, 14.38 mmol, 0.978 mL, 2 equiv.) in acetic acid (6.7 mL) was added dropwise at room temperature. After approximately 15 minutes the solution became homogeneous and turned a pale yellow. An additional 8 mL of acetic acid was then added and the solution allowed to stir for 24 hours at room temperature. The acetic acid was removed with mild heating (45^{o}C) under high vacuum. The pale yellow solid was emulsified in cold ethanol and cold filtered to yield a mixture of the meso and racemic 1,2-bis(phenylsulfinyl)ethane in 92% yield (2.088g). *Meso*-1,2-bis(phenylsulfinyl)ethane ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.52 (m, 10H), 3.05 (s,

4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.29, 131.55, 129.63, 124.10, 47.06. IR (neat) 3048.84, 2970.01, 2922.41, 1442.10, 1036.34, 745.45, 695.70 cm^{-1}.; *racemic*-1,2-bis(phenylsulfinyl)ethane. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 10H), 3.40 (m, 2H), 2.74 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.55, 131.53, 129.64, 124.08, 47.94. IR (neat, cm^{-1}) 3053.16, 2911.39, 1443.77, 1084.88, 1042.50, 748.52. HRMS (ESI) *m/z* calculated for $C_{14}H_{14}O_2S_2Na$ $[M+Na]^+$: 301.0333, found 301.0320.



1

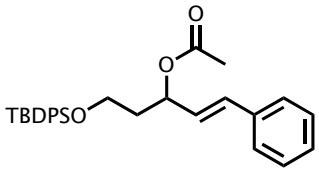
Catalyst 1: A flame dried 250 mL flask was charged with 2.53g (9.1 mmol) of 1,2-bis(phenylsulfinyl)ethane, 101 mL of CH_2Cl_2, and 2.04g (9.1 mmol) of $Pd(OAc)_2$. The mixture was stirred at 40°C for 24h. The reaction becomes a dark red homogenous reaction during the reaction time. The solution was concentrated *in vacuo* and dried with a stream of N_2 for 6 h to give a dark red solid used without further purification. **Note: The catalyst must be stored at below 4°C.** The catalyst slowly decomposes at ambient temperature; however, may be stored for prolonged periods (months) at reduced temperatures. ^1H NMR and IR data of this catalyst look like 1,2-bis(phenylsulfinyl)ethane ligand and $Pd(OAc)_2$. Trace amounts of phenyl vinyl sulfoxide can be observed by ^1H NMR (usually ~10% but can vary by +/-5%). We have noted suboptimal yields (e.g. 70% vs 90%) of Heck arylation with old bottles of $Pd(OAc)_2$. Recrystalization of $Pd(OAc)_2$ prior to complexation using the following procedure restores full activity of the catalyst.

$Pd(OAc)_2$ Recrystalization: "Old" $Pd(OAc)_2$ was dissolved in minimal refluxing benzene. A black precipitate was removed by hot Acrodisc® filtration. The resulting

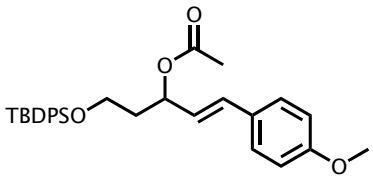
solution was cooled to room temperature without further manipulation. Amber crystals began to form after ~2 hours. After 24 hours the solution was filtered to give the recrystalized $Pd(OAc)_2$. A difference in NMR purity was noted between "old" and recrystalized $Pd(OAc)_2$ samples. Reported hydrogen values are normalized ratios of the smallest peak in the acetate region. "Old" $Pd(OAc)_2$ (see attached) ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 1H), 2.10 (s, 3.6H), 2.07 (s, 6.1H), 2.06 (s, 6.1H), 2.03 (m, 15.3H), 2.00 (m, 95.7H), 1.97 (s, 5.7H), 1.95 (s, 6.3), 1.89 (s, 9.4H). Recrystalized $Pd(OAc)_2$ (see attached) ^1H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.03 (s, 2.8H), 2.00 (s, 40.1H), 1.97 (s, 1.2H), 1.90 (s, 2.3H).

General Procedure for Tandem Allylic Oxidation/Vinylic Arylation: To a 40 mL borosilicate vial was added catalyst **1** (10 mol%, 0.1 mmol) and benzoquinone (2 equiv, 2 mmol). Olefin (1 equiv, 1 mmol) in dioxane (0.33M, 3mL), carboxylic acid (2-4 equiv, 2-4 mmol), and a stir bar were added sequentially. The olefin was weighed out in a 1 dram vial and transferred via dioxane (3 x 1 mL). The vial was capped and stirred at 45°C for 24-48 hours. The allylic oxidation was run until complete conversion of the α-olefin starting material was observed by GC or TLC. The vial was cooled to room temperature, and boronic acid (1.5 equiv, 1.5 mmol) was added to the reaction mixture using weighing paper. The vial was capped and stirred at room temperature for the indicated time. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 or hexane (2 times). The combined organics were washed with 5% aqueous K_2CO_3 (1 time), H_2O (1 time), and dried over $MgSO_4$. The mixture was

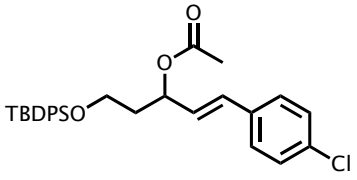
filtered and concentrated *in vacuo*. Purification by flash chromatography (EtOAc/hexanes mixtures) provided the pure product.



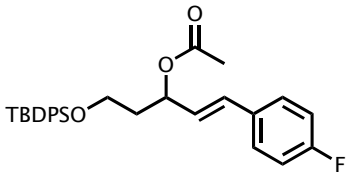
(*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-phenylpent-1-en-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyl(pent-4-enyloxy)diphenylsilane (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to 45^{o}C for 24 hours. Phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.) was added and heated to 45^{o}C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 4% ethyl acetate/hexanes as eluent to yield (*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-phenylpent-1-en-3-yl acetate as a clear oil. Run 1 (0.323 g, 0.705 mmol, 71%); run 2 (0.349 g, 0.761 mmol, 76%). **Average yield = 74%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.45-7.31 (m, 9H), 7.26 (m, 2H), 6.64 (d, J = 16 Hz, 1H), 6.15 (dd, J = 16, 7.5 Hz, 1H), 5.68 (ap q, J = 7 Hz, 1H), 3.75 (t, J = 6 Hz, 2H), 2.04 (s, 3H), 1.99 (m, 2H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 136.5, 135.8 (ap d), 133.8 (ap d), 132.9, 129.8 (ap d), 128.7, 128.1, 127.9 (ap d), 127.7, 126.8, 72.2, 60.0, 37.5, 27.0, 21.5, 19.4. IR (neat, cm^{-1}) 3070.72, 3050.07, 3027.54, 2957.36, 2931.20, 2857.85, 1738.12. HRMS (ESI) *m*/*z* calculated for $C_{29}H_{34}O_3SiNa$ $[M+Na]^+$: 481.2175, found 481.2171.



(*E*)-5-(*tert*-butyldiphenylsilyloxy) -1- (4-methoxyphenyl)pent -1- en -3- yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 1 equiv.), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyl(pent-4-enyloxy)diphenylsilane (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to 45^{o}C for 24 hours. 4-Methoxyphenylboronic acid (1.5 mmol, 228 mg, 1.5 equiv.) was added and stirred at room temperature for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield (*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-methoxyphenyl)pent-1-en-3-yl acetate as a clear oil. Run 1 (0.248 g, 0.508 mmol, 51%); run 2 (0.252 g, 0.515 mmol, 52%). **Average yield = 52%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.45-7.33 (m, 6H), 7.30 (ap d, *J* = 9 Hz, 2H), 6.85 (ap d, *J* = 8.5 Hz, 2H), 6.58 (d, *J* = 16 Hz, 1H), 5.99 (dd, *J* = 16, 8 Hz, 1H), 5.64 (ap q, *J* = 7 Hz, 1H), 3.82 (s, 3H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.02 (s, 3H), 1.96-1.88 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 159.6, 135.8 (ap d), 133.9, 133.8, 133.6, 132.6, 129.8 (ap d), 129.3, 128.0, 127.8, 125.4, 114.1, 72.5, 60.1, 55.5, 37.6, 27.0, 21.6, 19.4. IR (neat, cm^{-1}) 3071.10, 3046.59, 2956.80, 2931.89, 2857.75, 1737.61, 1608.13. HRMS (ESI) *m*/*z* calculated for $C_{30}H_{36}O_4SiNa$ $[M+Na]^+$: 511.2281, found 511.2276.

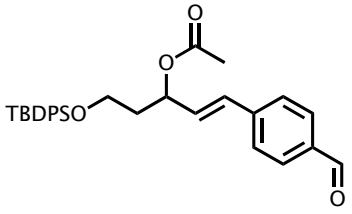


(*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-chlorophenyl)pent-1-en-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyl(pent-4-enyloxy)diphenylsilane (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv), and a stir bar. The mixture was heated to 45°C for 24 hours. 4-Chlorophenylboronic acid (1.5 mmol, 235 mg, 1.5 equiv.) was added and stirred at 45°C for 24 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-chlorophenyl)pent-1-en-3-yl acetate as a clear oil. Run 1 (0.305 g, 0.618 mmol, 62%); run 2 (0.313 g, 0.635 mmol, 64%). **Average yield = 63%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.45-7.33 (m, 6H), 7.27 (bs, 4H), 6.56 (d, J = 15.5 Hz, 1H), 6.10 (dd, J = 16, 7.5 Hz, 1H), 5.64 (ap q, J = 7.0 Hz, 1H), 3.72 (t, J = 5.5 Hz, 2H), 2.03 (s, 3H), 2.20-1.88 (m, 2H), 1.05 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 135.8, 135.7, 135.0, 133.8, 133.7, 131.5, 129.9, 129.8, 128.9, 128.4, 128.0, 127.9, 72.0, 59.9, 37.4, 27.0, 21.5, 19.4. IR (neat, cm^{-1}) 3074.93, 3049.09, 2931.36, 2858.11, 1738.37. HRMS (ESI) *m/z* calculated for $C_{29}H_{33}O_3ClSiNa$ $[M+Na]^+$: 515.1785, found 515.1775.



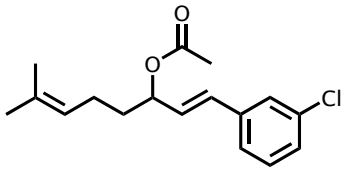
(*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-fluorophenyl)pent-1-en-3-yl acetate: To a 40 mL

borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyl(pent-4-enyloxy)diphenylsilane (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv), and a stir bar. The mixture was heated to 45°C for 24 hours. 4-Fluorophenylboronic acid (1.5 mmol, 210 mg, 1.5 equiv.) was added and stirred at 45°C for 7 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 5% ethyl acetate/hexanes as eluent to yield (*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-fluorophenyl)pent-1-en-3-yl acetate as a clear oil. Run 1 (0.3482 g, 0.732 mmol, 73%); run 2 (0.3508 g, 0.737 mmol, 74%). **Average yield = 74%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (m, 4H), 6.79-6.66 (m, 8H), 6.35 (ap t, *J* = 8.5 Hz, 2H), 5.97 (d, *J* = 16 Hz, 1H), 5.43 (dd, *J* = 16, 7.5 Hz, 1H), 5.05 (ap q, *J* = 7 Hz, 1H), 3.12 (t, *J* = 6 Hz, 2H), 1.43-1.30 (m, 2H), 1.39 (s, 3H), 0.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 163.6, 161.6, 135.7 (ap d), 133.7(ap d), 132.6 (ap d), 131.7, 129.8, 128.3 (ap d), 127.8, 127.4, 115.7, 115.5, 72.1, 59.9, 37.4, 27.0, 21.4, 19.3. IR (neat, cm^{-1}) 3071.40, 3043.92, 2950.90, 2931.20, 2858.02, 1737.30, 1601.84. HRMS (ESI) *m/z* calculated for $C_{29}H_{33}O_3FSiNa$ $[M+Na]^+$: 499.2081, found 499.2086.



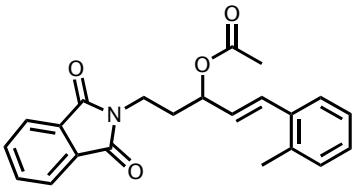
(*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-formylphenyl)pent-1-en-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyl(pent-4-

enyloxy)diphenylsilane (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to 45°C for 24 hours. 4-formylphenylboronic acid (1.5 mmol, 225 mg, 1.5 equiv.) was added and heated to 45°C for 5 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 15% ethyl acetate/hexanes as eluent to yield (*E*)-5-(*tert*-butyldiphenylsilyloxy)-1-(4-formylphenyl)pent-1-en-3-yl acetate as a clear oil. Run 1 (0.293 g, 0.602 mmol, 60%); run 2 (0.286 g, 0.588g, 59%). **Average yield = 60%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 7 Hz, 4H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.43-7.34 (m, 6H), 6.65 (d, *J* = 16.5 Hz, 1H), 6.31 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.68 (ap q, *J* = 7.0 Hz, 1H), 3.75 (t, *J* = 5.5 Hz, 2H), 2.05 (s, 3H), 2.06-1.91 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 170.4, 142.6, 135.8, 135.7, 133.7, 133.6, 131.6, 131.3, 130.3, 129.9 (ap d), 127.9, 127.3, 71.8, 59.9, 37.4, 27.0, 21.4, 19.4. IR (neat, cm^{-1}) 3071.13, 3048.95, 2957.46, 2931.26, 28.57.81, 2737.53, 1738.21, 1698.58. HRMS (ESI) *m/z* calculated for $C_{30}H_{34}O_4SiNa$ $[M+Na]^+$: 509.2124, found 509.2125.



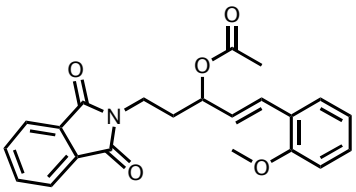
(*E*)-1-(3-Chlorophenyl)-7-methylocta-1,6-dien-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 7-methyl-1,6-octadiene (1 mmol, 124 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to

45°C for 48 hours. 3-Chlorophenylboronic acid (1.5 mmol, 235 mg, 1.5 equiv.), benzoquinone (1 mmol, 183 mg, 1 equiv.), acetic acid (1 mmol, 60 mg, 1 equiv.) were added and heated to 45°C for 6 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 4% ethyl acetate/hexanes as eluent to yield (*E*)-1-(3-Chlorophenyl)-7-methyl-1,6-octadien-3-acetate as a clear oil. Run 1 (0.178 g, 0.606 mmol, 61%); run 2 (0.193 g, 0.654 mmol, 65%). **Average yield = 63%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.22 (m, 3H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.13 (dd, *J* = 16.4, 7.6 Hz, 1H), 5.38 (ap q, *J* = 6.4 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 2.08 (s, 3H), 2.05 (m, 2H),1.77 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.5, 134.7, 132.7, 131.2, 130.0, 129.5, 128.0, 126.6, 125.0, 123.3, 74.2, 34.6, 25.9, 23.9, 21.5, 17.9. IR (neat, cm^{-1}) 2967.04, 2928.00, 2858.35, 1738.54, 1594.59, 1566.65. HRMS (ESI) *m*/*z* calculated for $C_{17}H_{21}O_2ClNa$ $[M+Na]^+$: 315.1128, found 315.1133.



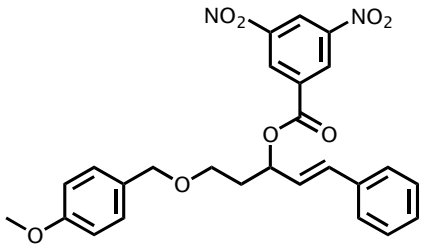
(*E*)-5-(1,3-dioxoisoindolin-2-yl)-1-*o*-tolylpent-1-en-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 2-(pent-4-enyl)isoindoline-1,3-dione (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to 45°C for 48 hours. *o*-Tolylphenylboronic acid (2 mmol, 272 mg, 1.5 equiv.), benzoquinone (1 mmol, 108 mg, 1 equiv.), and acetic acid (1 mmol, 60 mg, 1 equiv.) were added and heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat.

aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (*E*)-5-(1,3-dioxoisoindolin-2-yl)-1-*o*-tolylpent-1-en-3-yl acetate as a white powder. Run 1 (0.274 g, 0.749 mmol, 75%); run 2 (0.258 g, 0.706 mmol, 71%). **Average yield = 73%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.69 (m, 2H), 7.36 (m, 1H), 7.12 (m, 3H), 6.87 (d, *J* = 16 Hz, 1H), 6.00 (dd, *J* = 16, 7.2 Hz, 1H), 5.44 (ap q, *J* = 6.4 Hz, 1H), 3.81 (m, 2H), 2.34 (s, 3H), 2.15 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.4, 136.0, 135.3, 134.2, 132.2, 131.3, 130.5, 128.1, 127.9, 126.2, 125.8, 123.4, 72.6, 34.5, 33.1, 21.4, 20.0. IR (neat, cm^{-1}) 3061.90, 3020.60, 2946.33, 1772.19, 1738.23, 1714.39. HRMS (ESI) *m/z* calculated for $C_{22}H_{21}O_4NNa$ $[M+Na]^+$: 386.1368, found 386.1375.



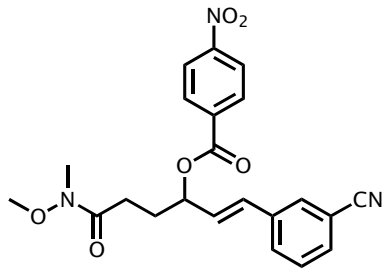
(*E*)-5-(1,3-dioxoisoindolin-2-yl)-1-(2-methoxyphenyl)pent-1-en-3-yl acetate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 2-(pent-4-enyl)isoindoline-1,3-dione (1 mmol, 325 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), and a stir bar. The mixture was heated to 45^{o}C for 48 hours. 2-Methoxyphenylboronic acid (1.5 mmol, 228 mg, 1.5 equiv.), benzoquinone (1 mmol, 108 mg, 1 equiv.), and acetic acid (1 mmol, 60 mg, 1 equiv.) were added and stirred at room temperature for 5 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with H_2O

(75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (*E*)-5-(1,3-dioxoisoindolin-2-yl)-1-(2-methoxyphenyl)pent-1-en-3-yl acetate as a clear oil. Run 1 (0.201 g, 0.530 mmol, 53%); run 2 (0.211 g, 0.556 mmol, 56%). **Average yield = 55%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.36 (d, *J* = 6.5 Hz, 1H), 7.19 (t, *J* = 8 Hz, 1H), 6.93 (d, *J* = 16.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.19 (dd, *J* = 16, 7.5 Hz, 1H), 5.44 (ap q, *J* = 5.5 Hz, 1H), 3.87-3.74 (m, 5H), 2.16-2.07 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 168.4, 157.1, 134.1, 132.2, 129.2, 128.1, 127.3, 127.2, 125.1, 123.3, 120.6, 110.9, 72.8, 55.5, 34.5, 33.0, 21.4. IR (neat, cm^{-1}) 2941.06, 2838.34, 1772.05, 1738.07, 1714.00, 1598.14. HRMS (ESI) *m/z* calculated for $C_{22}H_{21}NO_5Na$ $[M+Na]^+$: 402.1317, found 402.1327.



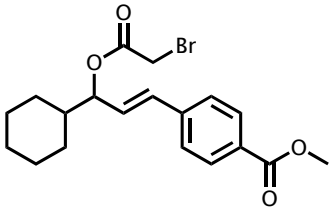
(*E*)-5-(4-methoxybenzyloxy)-1-phenylpent-1-en-3yl 3,5-dinitrobenzoate): To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 5-(4-methoxybenzyloxy)-1-pentene (1 mmol, 206 mg, 1 equiv.) in dioxane (3mL), 3,5-dinitrobenzoic acid (4 mmol, 848 mg, 4 equiv.), and a stir bar. The mixture was heated to 45^{o}C for 48 hours. Phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), benzoquinone (1 mmol, 108 mg, 1 equiv.), and acetic acid (1 mmol, 60 mg, 1 equiv.) were then added to the reaction, followed by heating to 45^{o}C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with methylene chloride (2 x 75 mL). The organic

layers were combined and rinsed with 5% K_2CO_3 (75 mL), H_2O (75 mL), and dried with $MgSO_4$. The filtered organic solution was concentrated via rotary evaporator. The crude yellow oil was further purified via silica chromatography (400 mL SiO_2) with 14% ethyl acetate/14% methylene chloride/hexanes as eluent to give (*E*)-1-Phenyl-5-(4-methoxybenzyloxy)-1-penten-3-(3,5-dinitrobenzoate) as a yellow solid. Run 1 (0.269 g, 0.55 mmol, 55%); run 2 (0.253 g, 0.51 mmol, 51%). **Average yield = 53%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (m, 1H), 9.02 (d, *J* = 1.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 8 Hz, 2H), 7.27 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 16 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.23 (dd, *J* = 16, 7.5 Hz, 1H), 5.93 (m, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 11 Hz, 1H), 3.70 (s, 3H), 3.61 (m, 2H), 2.27 (m, 1H), 2.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.1, 148.5, 135.9, 134.5, 134.4, 130.1, 129.7, 129.5, 128.8, 128.6, 126.9, 126.1, 122.2, 113.6, 75.8, 72.9, 65.7, 55.3, 34.8. IR (neat, cm^{-1}) 3101.83, 2934.64, 2863.07, 1730.84, 1544.89. HRMS (ESI) *m*/*z* calculated for $C_{26}H_{24}O_8N_2Na$ $[M+Na]^+$: 515.1430, found 515.1436.



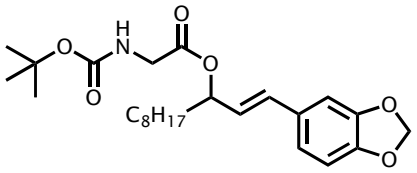
(*E*)-1-(3-cyanophenyl)-6-(methoxy(methyl)amino)-6-oxohex-1-en-3-yl 4-nitrobenzoate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *N*-methoxy-*N*-methylhex-5-enamide (1 mmol, 157 mg, 1 equiv.) in dioxane (3mL), *p*-nitrobenzoic acid (2 mmol, 334 mg, 2 equiv.), and a stir bar. The mixture was heated to 45°C for 48 hours. 3-cyanophenylboronic acid (1.5 mmol, 220 mg, 1.5 equiv.), benzoquinone (1 mmol, 108 mg, 1 equiv.), and acetic acid (1 mmol, 60 mg, 1 equiv.)

were added and heated to 45°C for 7 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, rinsed with 5% K_2CO_3 (75mL), H_2O (75 mL) and dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 50% ethyl acetate/hexanes as eluent to yield (*E*)-1-(3-cyanophenyl)-6-(methoxy(methyl)amino)-6-oxohex-1-en-3-yl 4-nitrobenzoate as a clear oil. Run 1 (0.320 g, 0.757 mmol, 76%); run 2 (0.328 g, 0.776 mmol, 78%). **Average yield = 77%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5 Hz, 2H), 8.23 (d, *J* = 9 Hz, 2H), 7.66 (s, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.43 (ap t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 16 Hz, 1H), 6.31 (dd, *J* = 16, 7 Hz, 1H), 5.75 (ap q, *J* = 7 Hz, 1H), 3.63 (s, 3H), 3.14 (s, 3H), 2.60 (t, *J* = 7, 2H), 2.27 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 164.1, 150.8, 137.4, 135.7, 131.6, 131.5, 131.0 (ap d), 130.3, 129.7, 129.5, 123.8, 118.7, 113.1, 75.8, 61.4, 32.4, 29.3, 27.7. IR (neat, cm^{-1}) 3110.89, 3078.75, 2938.96, 2230.86, 1724.36, 1660.20. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{22}O_6N_3$ $[M+H]^+$: 424.1509, found 424.1505.



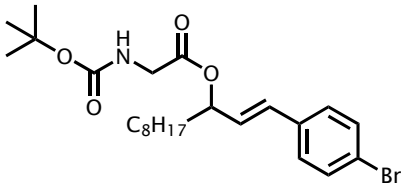
(*E*)-methyl 4-(3-(2-bromoacetoxy)-3-cyclohexylprop-1-enyl)benzoate: To a 40 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), allylcyclohexane (1 mmol, 124 mg, 1 equiv.) in dioxane (3mL), bromoacetic acid (4 mmol, 556 mg, 4 equiv.), and a stir bar. The mixture was heated to 45°C for 48 hours. 4-methoxycarbonylphenylboronic acid (1.5 mmol, 270 mg, 1.5 equiv.), benzoquinone (1 mmol, 108 mg, 1 equiv.), and acetic acid (1 mmol, 60 mg, 1

equiv.) were added and heated to 45°C for 24 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL). The organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (140 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield (*E*)-methyl 4-(3-(2-bromoacetoxy)-3-cyclohexylprop-1-enyl)benzoate as a clear oil. Run 1 (0.247 g, 0.627 mmol, 63%); run 2 (0.234 g, 0.595 mmol, 60%). **Average yield = 62%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 6.66 (d, *J* = 15.5 Hz, 1H), 6.23 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.26 (ap t, *J* = 7.5 Hz, 1H), 3.91 (s, 3H), 3.87 (d, *J* = 3 Hz, 2H), 1.86-1.67 (m, 6H), 1.29-1.02 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.8, 140.8, 133.1, 130.1, 129.6, 128.4, 126.7, 80.9, 52.3, 42.0, 28.9, 28.7, 26.4 (ap d), 26.0 (ap d). IR (neat, cm^{-1}) 2929.53, 2853.45, 1720.77. HRMS (ESI) *m*/*z* calculated for $C_{19}H_{23}O_4BrNa$ $[M+Na]^+$; 417.0677, found 417.0683.



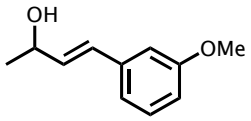
(*E*)-1-(benzo[*d*][1,3]dioxol-5-yl) undec -1- en -3- yl 2-(*tert*-butoxycarbonyl) acetate: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 1-undecene (1 mmol, 154 mg, 1 equiv.) in dioxane (3mL), *N*-Boc-glycine (2 mmol, 350 mg, 2 equiv.), and a stir bar. The mixture was heated to 45°C for 24 hours. 3,4-Methylenedioxyphenylboronic acid (1.5 mmol, 249 mg, 1.5 equiv.) was added and stirred at room temperature for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL). The organic layers were combined, rinsed with 60 mL of 5% K_2CO_3 (aq.) soluction, and dried over $MgSO_4$. After concentration, the

crude product was purified via silica gel chromatography (125 mL SiO_2) with 15% ethyl acetate/.5% triethylamine/hexanes as eluent to yield (*E*)-1-(benzo[*d*][1,3]dioxol-5-yl)undec-1-en-3-yl 2-(*tert*-butoxycarbonyl)acetate as a pale oil. NOTE: Product was found to be slightly unstable to silica gel unless buffered. Run 1 (0.3106 g, 0.695 mmol, 70%); run 2 0.3001 g, 0.671 mmol, 67%). **Average yield = 69%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.81 (d, *J* = 8 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.53 (d, *J* = 16 Hz, 1H), 5.96 (s, 2H), 5.93 (dd, *J* = 16, 8Hz, 1H), 5.42 (ap q, *J* = 7 Hz, 1H), 5.01 (m, 1H), 3.96 (dd, *J* = 18.5, 6 Hz, 1H), 3.89 (dd, *J* = 18, 5.5 Hz, 1H), 1.75-1.65 (m, 2H), 1.45 (s, 9H), 1.35-1.22 (m, 12H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.9, 148.2, 147.8, 133.1, 130.8, 125.5, 121.8, 108.5, 105.9, 101.3, 80.1, 76.6, 42.8, 34.8, 32.0, 29.6, 29.5, 29.4, 28.5, 25.4, 22.9, 14.3. IR (neat, cm^{-1}) 3392.35, 2928.61, 2857.15, 1744.28, 1715.64, 1505.27. HRMS (ESI) *m/z* calculated for $C_{25}H_{37}NO_6Na$ $[M+Na]^+$; 470.2519, found 470.2509.



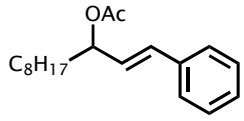
(*E*)-1-(4-Bromophenyl)undec-1-en-3-yl 2-(*tert*-butoxycarbonyl) acetate: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 1-undecene (1 mmol, 154 mg, 1 equiv.) in dioxane (3mL), *N*-Boc-glycine (2 mmol, 350 mg, 2 equiv.), and a stir bar. The mixture was heated to 45^{o}C for 24 hours. 4-Bromophenylboronic acid (1.5 mmol, 301 mg, 1.5 equiv.) was added and heated to 45^{o}C for 5 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was

purified via silica gel chromatography (140 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield (*E*)-1-(4-Bromophenyl)-1-undecen-3-*N*-boc-glycine as a pale oil. Run 1 (0.359 g, 0.746 mmol, 75%); run 2 0.360 g, 0.749 mmol, 75%). **Average yield = 75%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.42 (ap q, *J* = 6.8 Hz, 1H), 5.02 (bs, 1H), 3.92 (m, 2H), 1.70 (m, 2H), 1.44 (s, 9H), 1.34-1.85 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 155.8, 135.2, 131.9, 131.8, 128.3, 128.1, 122.0, 80.1, 76.1, 42.7, 34.6, 32.0, 29.6, 29.5, 29.4, 28.5, 25.3, 22.8, 14.3. IR (neat, cm^{-1}) 3369.70, 2928.07, 2856.25, 1747.79, 1716.11, 1508.35. HRMS (ESI) *m*/*z* calculated for $C_{24}H_{37}NO_4Br$ $[M+H]^+$: 482.1906, found 482.1911.



(*E*)-1-(3-Methoxyphenyl)-1-buten-3-ol: 1-Butene (0.112 g, 2 mmol, 0.178 mL, 1 equiv.) was condensed in a 25 mL graduated tube at -78°C. The liquid was transfered via cannula under a positive pressure of oxygen to a 40 mL sealed tube (cooled to -78°C). Dioxane (3mL, purged with O_2 for 30 minutes prior to use) was added to the graduated tube at -78°C (to trap any residual butene in the cannula), then warmed to the point when it could be transferred with cannule (with a positive pressure of O_2) to the sealed tube. To the sealed tube (maintained at -78°C) was added the following solids: Benzoquinone (0.432 g, 4 mmol, 2 equiv.), catalyst **1** (101 mg, 0.2 mmol, 10 mol%), 4-nitrobenzoic acid (1.00 g, 6 mmol, 3 equiv.). After addition of <u>each</u> solid, 1 mL of oxygenated dioxane was added and used to rinse the solid off of the sides of the sealed tube (3 mL total). The tube was sealed under an atmosphere of O_2, warmed to room temperature with stirring, and then heated to 45°C for 20h. The mixture

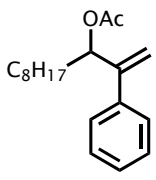
was cooled to room temperature, N_2 was bubbled through it for 5 minutes (to remove unreacted 1-butene). 3-Methoxyphenyl boronic acid (0.456 g, 3 mmol, 1.5 equiv.) was then added and heated in the sealed tube at 45°C. Reaction progress was monitored by TLC until disappearance of the allylic ester was observed (~4h). Upon completion the mixture was cooled to room temperature and diluted with 100 mL of a saturated aqueous potassium carbonate/methanol mixture (1:1) to effect hydrolysis of the *p*-nitrobenzyl ester. The reaction progress was again monitored by TLC. Upon completion (~4h) the mixture was diluted with 100 mL H_2O and extracted 2 x 100 mL CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$. Concentration via rotary evaporator yielded a crude mixture which was purified via silica gel chromatography (130 mL SiO_2) in 20% ethyl acetate/hexanes as eluent to afford (*E*)-1-(3-Methyoxyphenyl)-1-buten-3-ol as a clear oil. Run 1 (0.276 g, 1.55 mmol, 77%); run 2 (0.269 g, 1.34 mmol, 76%). **Average yield = 77%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 6.91 (t, *J* = 1.6, 1H), 6.80 (ddd, *J* = 8, 2.4, .4, 1H), 6.53 (d, *J* = 15.6, 1H), 6.26 (dd, *J* = 15.6, 6), 4.48 (ap dp, *J* = 6.4, .4, 1H), 3.81 (s, 3H), 1.78 (bs, 1H), 1.37 (d, *J* = 6.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ159.9, 138.3, 134.0, 129.8, 129.4, 119.3, 113.5, 111.9, 69.1, 55.4, 23.6. IR (neat, cm^{-1}) 3368.94, 2970.20, 2930.23, 2835.91, 1598.23, 1580.15. HRMS (ESI) *m/z* calculated for $C_{11}H_{14}O_2Na$ $[M+Na]^+$: 201.0891, found 201.0889.



(*E*)-1-phenylundec-1-en-3-yl acetate: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%) or palladium acetate (0.1 mmol, 22.4 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2

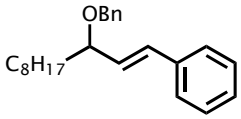
equiv.), undec-1-en-3-yl acetate (1 mmol, 212 mg, 1 equiv.) in dioxane (3mL), acetic acid 4 equiv. (4 mmol, 24.0 mg, 0.231 mL) or 1 equiv. (1 mmol, 60.0 mg, 58 μl), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.) and a stir bar. After heating to 45°C for 4 hours, the mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL). The organic layers were combined, rinsed with 60 mL of 5% K_2CO_3 (aq.) solution, and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 5% ethyl acetate/hexanes as eluent to yield (*E*)-1-phenylundec-1-en-3-yl acetate as a colorless oil. All yields are the average of 2-3 runs. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 6.59 (d, *J* = 16 Hz, 1H), 6.12 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.39 (ap q, *J* = 7.2 Hz, 1H), 2.08 (s, 3H), 1.76-1.61 (m, 2H), 1.35-1.22 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 136.6, 132.7, 128.8, 128.1 (ap d), 126.8, 75.1, 34.8, 32.1, 29.7, 29.6, 29.5, 25.4, 22.9, 21.6, 14.4. IR (neat, cm^{-1}) 2926.47, 2856.91, 1737.89, 1237.51 HRMS (EI) *m/z* calculated for $C_{19}H_{28}O_2$ $[M]^+$; 288.2089, found 288.2088.

NOTE: 2,6-Dimethylbenzoquinone (2 mmol, 272.0 mg, 2 equiv.) may be used instead of benzoquinone to yield (*E*)-1-phenylundec-1-en-3-yl acetate as a colorless oil (0.268 g, 0.932 mmol, 93%) with >20:1 E:Z selectivities by crude ^{1}H NMR and 66:1 internal:terminal olefin selectivities by crude GC analysis.



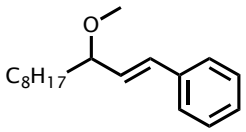
2-phenylundec-1-en-3-yl acetate: Terminal olefin standard. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.35-7.29 (m, 3H), 5.67 (t, *J* = 6 Hz, 1H), 5.28 (ap d, *J* = 6 Hz, 2H), 2.12 (s, 3H), 1.61 (ap q, *J* = 6.4 Hz, 2H), 1.30-1.20 (m, 12H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 170.6, 148.8,

139.8, 128.5, 127.9, 127.2, 113.8, 75.8, 34.1, 32.0, 29.6, 29.4 (ap d), 25.6, 22.8, 21.5, 14.3. IR (neat, cm^{-1}) 2953.63, 2927.47, 2856.50, 1741.83, 1237.16. HRMS (EI) *m/z* calculated for $C_{19}H_{28}O_2$ $[M]^+$: 288.2089, found 288.2091.



(*E*)-1-((1-phenylundec-1-en-3-yloxy)methyl)benzene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 1-((undec-1-en-3-yloxy)methyl)benzene (1 mmol, 260 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-1-((1-phenylundec-1-en-3-yloxy)methyl)benzene as a clear oil. Run 1 (0.308 g, 0.923 mmol, 92%); run 2 (0.305 g, 0.914 mmol, 91%). **Average yield = 92%.** The Heck arylation may also be performed at room temperature for 4h: run 1 (0.309 g, 0.924 mmol, 92%); run 2 (0.311 g, 0.931, 93%). **Average yield = 93%.** By crude ^1H NMR all selectivities were >20:1 E:Z and >20:1 internal olefin : terminal olefin. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.2 Hz, 2H), 7.36-7.26 (m, 8H), 6.53 (d, J = 15.6 Hz, 1H), 6.13 (dd, J = 16, 8 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.41 (d, J = 12 Hz, 2H), 3.90 (q, J = 8 Hz, 1H), 1.80-1.71 (m, 1H), 1.63-1.54 (m, 1H), 1.46-1.26 (m, 12H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.9, 132.5, 131.04, 128.9, 128.6, 128.0, 127.9, 127.7, 126.7, 80.4, 70.3, 36.2,

32.1, 29.9, 29.8, 29.6, 25.8, 22.9, 14.4. IR (neat, cm^{-1}) 3025.86, 2952.73, 2926.76, 2852.95. HRMS (CI) *m/z* calculated for $C_{24}H_{33}O$ $[M+H]^+$: 337.2532, found 337.2538.

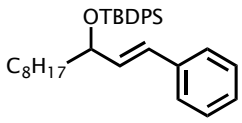


(*E*)-1-(3-methoxyundec-1-enyl)benzene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 3-methoxyundec-1-ene (1 mmol, 184 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-1-(3-methoxyundec-1-enyl)benzene as a clear oil. Run 1 (0.246 g, 0.946 mmol, 95%); run 2 (0.247 g, 0.951 mmol, 95%). **Average yield = 95%.** Heck arylation may also be performed at room temperature for 4h: run 1 (0.243 g, 0.936 mmol, 94%); run 2 (0.235 g, 0.904 mmol, 90%). **Average yield = 92%.** By crude ^1H NMR all selectivities were >20:1 E:Z and >20:1 internal olefin : terminal olefin. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 16 Hz, 1H), 6.06 (d, *J* = 15.6, 8 Hz, 1H), 3.70 (q, *J* = 7.6 Hz, 1H), 3.33 (s, 3H), 1.74-1.66 (m, 1H), 1.60-1.52 (m, 1H), 1.44-1.20 (m, 12H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 132.4, 130.7, 128.8, 127.8, 126.6, 82.9, 56.4, 36.0, 32.1, 29.9, 29.8, 29.5, 25.6, 22.9, 14.3. IR (neat, cm^{-1}) 2957.02,

2928.01, 2923.33, 2854.66. HRMS (CI) *m/z* calculated for $C_{18}H_{29}O$ $[M+H]^+$: 261.2218, found 261.2216.

Arylation of 3-methyl-hex-1-ene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 3-methylhex-1-ene (1 mmol, 98.2 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 100% hexanes as eluent to yield an inseparable mixture of isomers as a clear oil. Note: Due to volatility concerns, the hexanes was removed via rotary evaporator at 0°C. By crude ^{1}H NMR the ratio of internal olefin : trisubstituted olefin : terminal olefin at 45°C is 8:1:1. Run 1 (0.129 g, 0.742 mmol, 74%); run 2 (0.132 g, 0.759 mmol, 76%). **Average yield = 75%.** Heck arylation may also be performed at room temperature for 4h: run 1 (0.134 g, 0.777 mmol, 78%). **Yield = 78%.** By crude ^{1}H NMR the room temperature ratio of internal olefin : trisubstituted olefin : terminal olefin, 10:7:1. By crude ^{1}H NMR all selectivities were >20:1 E:Z. ^{1}H NMR (400 MHz, $CDCl_3$) δ Internal olefin: 6.34 (d, J = 16 Hz, 1H), 6.10 (dd, J = 16, 8 Hz, 1H), 2.31 (m, 1H). Trisubstituted olefin: 5.35 (t, J = 7.2 Hz, 1H), 3.37 (d, J = 7.2 Hz, 2H). Terminal olefin: 5.18 (s, 1H), 5.03 (s, 1H), 2.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ Internal olefin: 138.2, 137.3, 128.7, 128.1, 127.0, 126.2, 39.6,

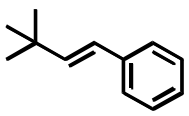
37.3, 20.9, 20.7, 14.4. HRMS (CI) *m/z* calculated for $C_{13}H_{19}$ $[M+H]^+$: 175.1487, found 175.1488.



(*E*)-*tert*-butyldiphenyl(1-phenylundec-1-en-3-yloxy)silane: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), *tert*-butyldiphenyl(undec-1-en-3-yloxy)silane (1 mmol, 409 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-*tert*-butyldiphenyl(1-phenylundec-1-en-3-yloxy)silane as a pale yellow oil. Run 1 (0.459 g, 0.948 mmol, 95%); run 2 (0.451 g, 0.930 mmol, 93%). **Average yield = 94%.** Heck arylation may also be performed at room temperature for 4h: run 1 (0.478 g, 0.989 mmol, 99%), run 2 (0.479 g, 0.991 mmol, 99%). **Average yield = 99%.** By crude ^{1}H NMR all selectivities were >20:1 E:Z and >20:1 internal olefin : terminal olefin. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 13.6, 7.2 Hz, 4H), 7.43-7.21 (m, 11H), 6.21 (d, *J* = 16 Hz, 1H), 6.13 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.29 (ap q, *J* = 5.6 Hz, 1H), 1.65-1.47 (m, 2H), 1.30-1.18 (m, 12H), 1.09 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 136.2, 136.1, 135.7, 134.7, 134.5, 133.0, 129.8, 129.7, 129.6, 128.6, 127.7, 127.6, 127.4, 126.6, 74.8, 38.2, 32.1, 29.7 (app d), 29.5, 27.3, 24.9, 22.9, 19.6, 14.4. IR (neat, cm^{-1}) 2957.98,

2958.12, 2927.73, 2856.35. HRMS (CI) *m/z* calculated for $C_{34}H_{45}OSi$ $[M+H]^+$: 485.3240, found 485.3238.

Arylation of 1-undecene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 1-undecene (1 mmol, 98.2 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 100% hexanes as eluent to yield (*E*)-1-(3-methylhex-1-enyl)benzene as a clear oil (0.137 g, 0.603 mmol, 60%). **Yield = 60%.** By crude ^{1}H NMR the ratio of products was determined to be 4:1:1. Heck arylation may also be preformed at room temperature for 4h (0.140 g, 0.612 mmol, 61%). **Yield = 61%.** By crude ^{1}H NMR the ratio of internal olefin : allylic benzene : terminal olefin was found to be 4:3:1. By crude ^{1}H NMR E:Z selectivities were found to be >20:1 in all cases. ^{1}H NMR (400 MHz, $CDCl_3$) δ Internal olefin: 6.43 (d, *J* = 15.6 Hz, 1H), 6.28 (dt, *J* = 16, 6.8 Hz, 1H), 2.25 (q, *J* = 7.6 Hz, 2H). Allylic benzene: 5.66-5.52 (m, *2*H), 3.38 (d, *J* = 6 Hz, 2H), 2.07 (q, *J* = 6.4 Hz, 2H). Terminal olefin: 5.31 (s, 1H), 5.10 (s, 1H), 2.55 (t, *J* = 6.8 Hz, 2H).



(*E*)-1-(3,3-dimethylbut-1-enyl)benzene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%),

benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 3,3-dimethyl-1-butene (1 mmol, 84.2 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), phenylboronic acid (1.5 mmol, 183 mg, 1.5 equiv.), and a stir bar. The mixture was heated to 45°C for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH_4Cl and extracted with hexanes (2 x 75 mL) and rinsed with 5% K_2CO_3 (1 x 75 mL). The organic layers were combined and dried over $MgSO_4$. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO_2) with 100% hexanes as eluent to yield (*E*)-1-(3,3-dimethylbut-1-enyl)benzene as a clear oil. Run 1 (0.158 g, 0.999 mmol, quantitative); run 2 (0.158 g, 1.000 mmol, quantitative). **Average yield = quantitative.** By crude ^1H NMR all selectivities were >20:1 E:Z and >20:1 internal olefin : terminal olefin. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.34 (d, J = 16 Hz, 1H), 6.28 (d, J = 16 Hz, 1H), 1.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 138.2, 128.7, 126.9, 126.2, 124.7, 33.6, 29.8. IR (neat, cm^{-1}) 3025.38, 2960.48, 2903.23, 2866.92. HRMS (CI) *m*/*z* calculated for $C_{12}H_{17}$ $[M+H]^+$: 161.1330, found 161.1330.

Table 3, Entry 1:

Run 1 (287.1 mg, 0.997 mmol, 100%, 99:1 internal;terminal); run 2 (283.4 mg, 0.984 mmol, 98%, 97:3 internal:terminal); run 3 (272.6 mg, 0.947 mmol, 95%, 98:2 internal:terminal). **Average yield = 99%, 98:2.**

Table 3, Entry 2:

Run 1 (104.3 mg, 0.362 mmol, 36%); run 2 (107.3 mg, 0.372 mmol, 37%). **Average yield = 37%.**

Table 3, Entry 3:

Run 1 (20.2 mg, 0.070 mmol, 7%); run 2 (25.0 mg, 0.0868 mmol, 9%). **Average yield = 8%.**

Table 3, Entry 4:

Run 1 (193.5 mg, 0.672 mmol, 67%); run 2 (202.3 mg, 0.702 mmol, 70%); run 3 (219.6 mg, 0.762 mmol, 76%). **Average yield = 71%.** Note: Variation was observed for this entry based on catalyst batch. Batches containing move phenylvinyl sulfoxide (and presumably therefore acetic acid) show heightened reactivity toward the arylation without acetic acid added.

Table 4, Entry 5:

Run 1 (265.2 mg, 0.921 mmol, 92%); run 2 (272.6 mg, 0.947 mmol, 95%). **Average yield = 94%.**

1.5 REFERENCE

[1] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; Wiley-VCH: Weinheim, Germany, 1996.

[2] Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493.

[3] (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

[4] Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

[5] (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (c) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (d) Fraunhoffer, K. F.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (e) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 8217.

[6] Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178.

[7] Silicon: (a) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. Tin: (b) Hirabayashi, K.; Ando, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Synlett* **1999**, *99*. Boron: (c) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett*. **2001**, *3*, 3313. (d) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231.

[8] (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 2768. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317.

[9] Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005; p14.

[10] (a) Dong, Y.; Spittle, P.; Hoberg, J. O. *Tetrahedron Lett*. **2004**, *46*, 353. (b) Trost, B. M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, *128*, 2540. (c) Kazmair, U. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 998. (d) Kobayashi, M.; Masumoto, K.; Nakai, T. *Tetrahedron Lett*. **1996**, *37*, 3005.

[11] Edmondson, S. D.; Mastracchio, A.; Duffy, J. L.; Eiermann, G. J.; He, H.; Ita, I.; Leiting, B.; Leone, J. F.; Lyons, K. A.; Makarewicz, A. M.; Patel, R. A.; Petrov, A.; Wu, J. K.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3048.

[12] Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.

[13] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

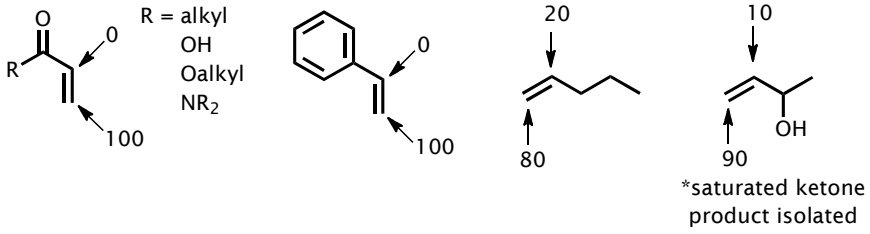
CHAPTER 2

A GENERAL AND HIGHLY SELECTIVE CHELATE-CONTROLLED INTERMOLECULAR OXIDATIVE HECK REACTION

2.1 INTRODUCTION

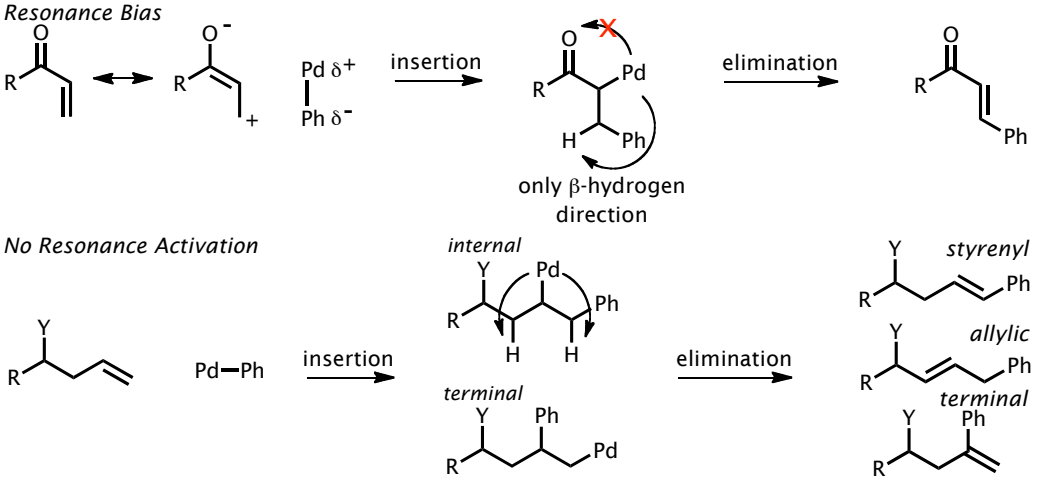
The intermolecular Heck reaction is unique among cross-coupling reactions in that it directly transforms vinylic C-H bonds of α-olefins to C-C bonds (figure 3).[1] The chemically inert nature of α-olefins allows for fewer synthetic steps by forgoing installation, protection, and oxidation state changes to preoxidized functionality throughout reaction sequences. Recently, the intermolecular Heck-arylation has enjoyed an increase in the scope of the arylating agent; however, the restricted α-olefin scope has prevented widespread application in complex molecule synthesis (figure 6).[2] Generally,

Figure 6. Insertion selectivities of various terminal olefins.



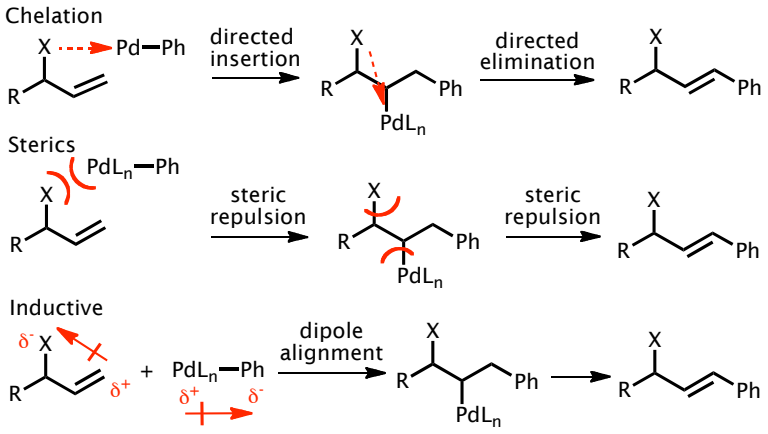
resonance bias on the α-olefin is necessary for controlling regioselectivity of insertion and β-hydride elimination as well as for improved reactivity (figure 7). The demand for resonance bias frequently limits the α-olefin component to α,β-unsaturated carbonyls, styrenes and enol ethers.

Figure 7. Resonance-aided selectivities.



We hypothesized that directing factors other than resonance activation could control the siteselectivities of insertion and β-hydride elimination under our oxidative Heck arylation conditions. A coordination event to an arylated palladium species could direct the orientation of olefin insertion and the direction of β-hydride elimination by restricting bond rotations (figure 8). Alternatively, steric bulk could control insertion by directing the relatively large aryl toward the more accessible terminus. However, the steric repulsion exerted on the palladium must be greater from the adjacent substitution

Figure 8. Non-resonance modes of selectivity.



than from the terminal aryl to guide β-hydride elimination. Finally, an electron withdrawing group could direct insertion and β-hydride elimination by creating electronic

dipoles on the olefin. This charge distribution could be used to align with the electronically dissymmetric palladium aryl intermediate.

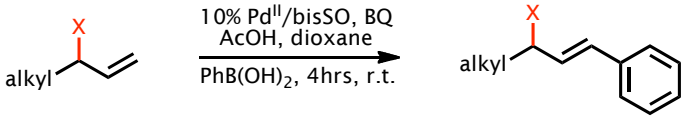
An oxidative Heck manifold is well suited for exploring these modes of selectivity. As previously mentioned, oxidative Heck reactions begin catalytic cycles with a transmetalation event rather than oxidative addition.[3] To effect transmetalation, electrophilic palladium (II) sources with weakly donating ligands are often used instead of the strongly donating ligands used with nucleophilic palladium (0) complexes.[4] A more electron deficient palladium aryl intermediate will coordinate more readily to heteroatoms and be more sensitive to inductive effects. Importantly, the remaining anionic ligand on the palladium-aryl intermediate will play a crucial role in determining the amount of steric influence applied by proximal functionality. Coordinating non-halide anionic ligands have the potential to increase the size of the palladium moiety compared to the halogen palladium moieties formed during oxidative addition. Our previously reported conditions for the sequential allylic C-H, vinylic C-H activation reaction (chapter 1), which uses a palladium (II) acetate complex, seemed amenable to these directing factors.

2.2 RESULTS AND DISCUSSION

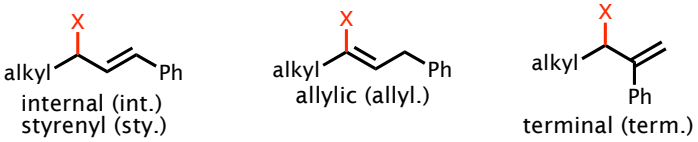
2.2.1 Understanding and Separating Directing Factors for Heck Arylations of Non-Resonance Activated Olefins

We began our studies of these hypothesized selectivity effects by examining allylic functionality and its relation to the siteselectivities of insertion and β-hydride elimination (table 4). A straight-chain hydrocarbon gave a baseline selectivity of 4:1 for

Table 4. Effect of allylic substitution on selectivities.



entry	X	isolated yield	int.:term.	sty.:allyl.
1	H	68%	4:1	1:1
2	OAc	98%	>20:1	>20:1
3	OMe	95%	>20:1	>20:1
4	NHBoc	98%	>20:1	>20:1
5	CF_3	62%	>20:1	>20:1
6	F,F	83%	>20:1	>20:1
7	Me	75%	4:1	8:1
8	*t*-Bu	79%	>20:1	>20:1
9	OTBDPS	94%	>20:1	>20:1

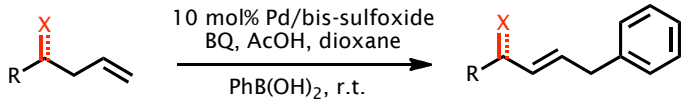


internal vs. terminal olefin isomers resulting from insertion and 1:1 styrenyl vs. allylic olefin isomers from β-hydride elimination (table 4, entry 1). As previously reported, allylic acetate functionality gave high selectivities possibly due to chelation, induction, and sterics (table 4, entry 2). Inductively withdrawing allylic chelators OMe and NHBoc also gave excellent isomer ratios (table 4, entries 3 & 4). Organofluorine is unlikely to strongly coordinate to palladium and also will exhibit a small steric influence. To test for inductive control, allylic difluoride and trifluoromethyl derivatives were tested (table 4, entries 5 & 6). Both furnished good selectivities, indicating that inductive direction is operative in controlling olefin selectivities. An allylic methyl group gave poor selectivity for insertion (4:1) but improved selectivities for β-hydride elimination (8:1 vs 1:1, table 4, entry 7) relative to unsubstituted olefin. This result suggests the reaction manifold is not controlled primarily by sterics, as the methyl group is larger than the allylic difluoride

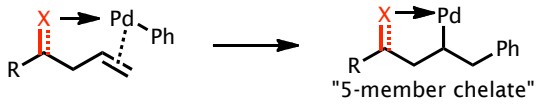
and methoxy ether but gives inferior isomer selectivities. When the steric bulk is increased to an allylic *t*-butyl or TBPDS ether excellent selectivities are observed which indicates substantial steric bulk is tolerated in this system and provides constitutional control (table 4, entries 8 & 9). Significantly, the allylic *t*-butyl group has little inductive effect and no possibility for chelation, suggesting steric control is operative if the directing group is large enough.

Having shown inductive and steric effects to be contributing directing factors, we began to examine the possibility of chelation control guiding the selectivities in this reaction.[5] Moving the directing functionality to the homoallylic position helps distinguish directing factors, since inductive and steric effects decrease dramatically the

Table 5. 5-member chelation control.



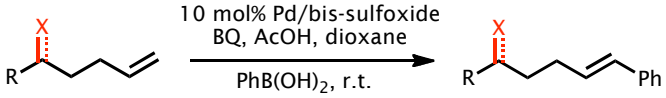
entry	X	R	yield	int.:term.	sty.:allyl.
1	H	alkyl	75%	4:1	1:1
2	OAc	alkyl	89%	9:1	2:1
3	OMe	alkyl	87%	9:1	1:1
4	NHBoc	alkyl	91%	17:1	14:1
5	O	OMe	64%	>20:1	1:4
6	O	Bn	51%	>20:1	1: >20



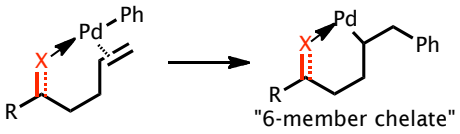
further they are from the reactive site. Homoallylic acetate and methyl ethers gave olefin isomer selectivities slightly better than a straight chained hydrocrabon (table 5, entries 2 &3). Employing a Boc protected amine in the same position gave higher selectivities (table 5, entry 4). Interestingly, electron rich homoallylic carbonyls favored β-hydride elimination out of conjugation with the aryl moiety to furnish α,β-unsaturated carbonyls with good insertion selectivities (table 5, entries 5 & 6).

Moving chelating functionality to the bis-homoallylic position (6-member chelate) allows for further examination of chelation control. Carbonyls in this position direct to give good selectivities and preparative yields of the styrenyl isomer (table 6, entries 2 and 3). These results suggest this oxidative Heck manifold is also under chelation control from electron rich functionality.

Table 6. 6-member chelation control.

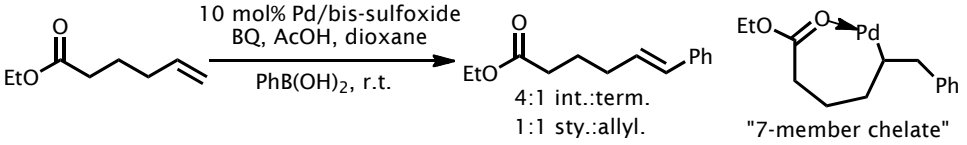


entry	X	R	yield	int.:term.	sty.:allyl.
1	NHBoc	alkyl	81%	4:1	1:1
2	O	OMe	68%	12:1	6:1
3	O	CH_3	50%	>20:1	>20:1



Finally, to confirm that chelation control is operative in this oxidative Heck-arylation, a potential 7-member chelate was attempted. As predicted, poor olefin regioselectivities were observed, similar to those for the straightchain hydrocarbon

Figure 9. 7-member chelation is not favorable.



(figure 9). This result indicates that no directing effects are operative for functionality capable of forming a relatively unfavorable 7-membered palladium chelate.

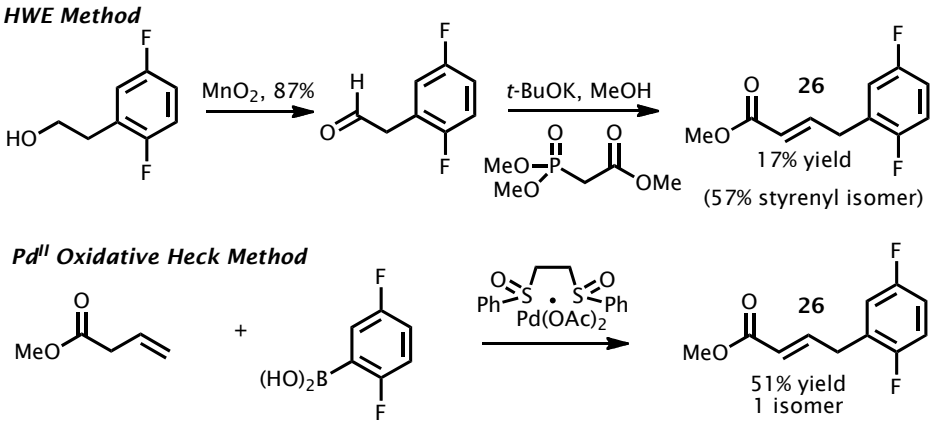
2.2.2 State-of-the-Art Synthesis of γ-Arylated-α,β-Unsaturated Carbonyls

Having found chelation, induction, and sterics to all be directing factors for the palladium (II)/bis-sulfoxide catalyzed oxidative Heck-arylation, we began examining the

applications of this system in complex molecule synthesis. β-Amino acids are desirable biological structures due to applications as enzyme inhibitors,[6] unique peptide folding,[7] and potentially as medicinal agents for overcoming antibiotic resistance. The α,β-unsaturated carbonyl moiety is known to undergo enantioselective conjugate addition of chiral amines and azide anion to form the β-amino acid precursor.[8] When trying to access a γ-arylated-β-amino acid, workers at Merck attempted to synthesize the γ-arylated-α,β-unsaturated methyl ester intermediate **26**.[9] However, useful yields could not be isolated due to the instability of the desired product under the reaction conditions used since light, base, acid, and heat all isomerize the desired product to the more thermodynamically stable styrenyl olefin isomer. The attempted Horner-Wadsworth-Emmons (HWE) reaction route relies on condensation of a phosphonate ester with a benzyl aldehyde. Electron deficient benzyl aldehydes are frequently problematic to prepare due to facile polymerization, even under seemingly mild conditions. Furthermore, the HWE reaction conditions employ potassium *tert*-butoxide as base to promote addition to the benzyl aldehyde. The strong base used in the HWE reaction caused isomerization to the undesired styrenyl isomer giving only 17% of the desired α,β-unsaturated isomer as a difficult to separate 1:3 mixture favoring the undesired isomer (figure 10). Ultimately, Merck was forced to abandon the desired route to the target compound. Under the newly discovered oxidative Heck conditions, the desired α,β-unsaturated product was formed in preparative yields as a single isomer from two commercially available compounds. The mild nature of this reaction manifold is illustrated by no erosion of the desired α,β-unsaturated product to the styrenyl isomer.

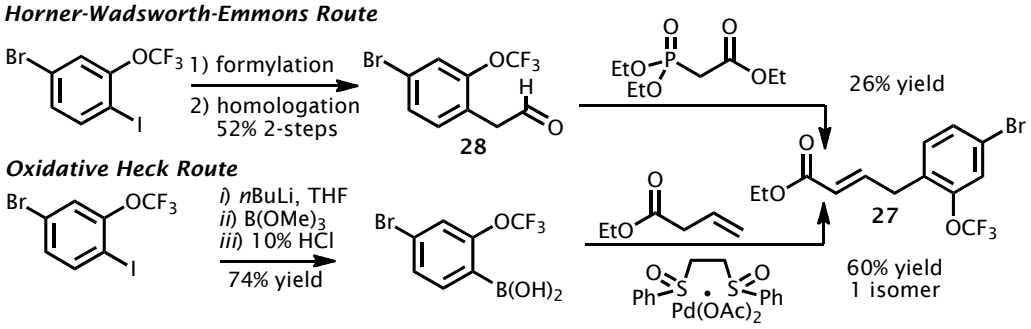
To the best of our knowledge, this is the only efficient method for forming γ-arylated-α,β-unsaturated esters with electron withdrawn aryl moieties.

Figure 10. γ-arylated-β-amino acid precursors.



Melanin-concentrating hormone (MCH) antagonist are capable of regulating appetite[10] and functioning as antidepressants.[11] One of the MCH antagonist small molecules being investigated is formed via the α,β-unsaturated-γ-arylated ethyl ester intermediate **27**.[12] The Arena group accessed this intermediate by HWE condensation with benzyl aldehyde **28** in three steps from commercial materials (figure 11). Despite a poor yield for the key HWE step (26%), the route was still used as it allowed rapid access

Figure 11. Synthesis of a MHC through a γ-arylated-α,β-unsaturated ester intermediate.

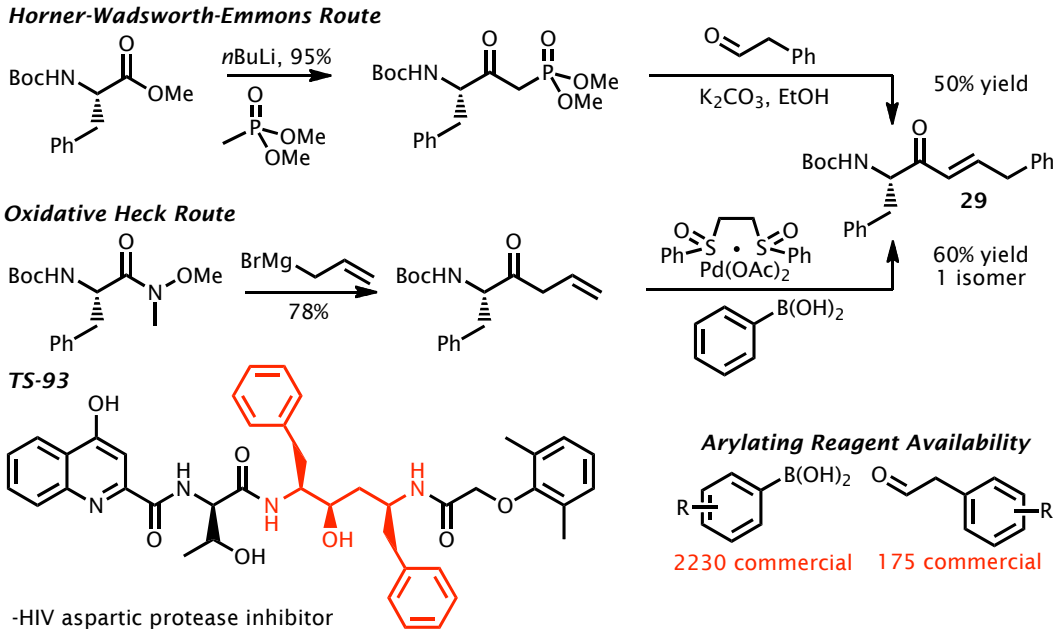


to the desired motif. In general, HWE reactions are predominantly used to access these types of intermediates in spite of poor selectivities and yields for the desired products. Under our oxidative Heck arylation conditions, the desired product was formed as the

only observed isomer in two steps from commercial materials with the key arylation step proceeding in 60% yield.

Aspartic proteases help determine the pathogenicity of both viruses and fungi; therefore, aspartic inhibitors are possible treatments for HIV and other infections.[13] The HIV aspartic protease inhibitor intermediate to TS-93, **29**, was synthesized in two steps with the key HWE reaction proceeding in 50% yield (figure 12).[14] α,β-unsaturated-γ-arylated ketone intermediates to medicinally interesting molecules are often conveniently synthesized in preparative yields through HWE reactions due to a weaker base being employed (potassium carbonate vs potassium *tert*-butoxide for ester equivalents). However, only electron rich or electron neutral aryls are amenable to this reaction because product olefin isomerization is still problematic for electron deficient aryls. The step count and yield are comparable to the oxidative Heck route (2 steps, 60% for the key

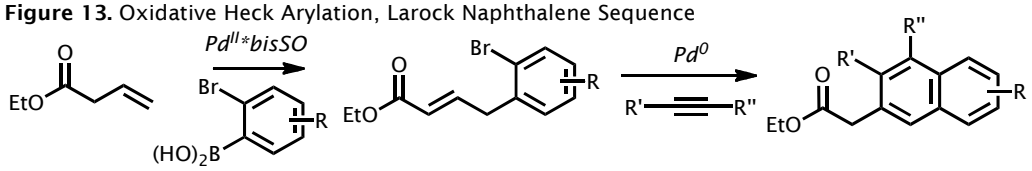
Figure 12. HIV aspartic protease inhibitor.



arylation step). However, 2230 aryl boronic acids are commercially available which gives a tremendous advantage toward rapid diversification options over the HWE route since only 175 benzyl aldehydes are commercially available.

Larock has developed a palladium (0)-based naphthalene synthesis from γ-arylated-α,β-unsaturated carbonyls where the aryl ring must be substituted at the ortho position with a halide (figure 13).[15] Under our palladium (II)-based conditions, halides are preserved through the reaction, which allows for a complementary palladium (0)-

Figure 13. Oxidative Heck Arylation, Larock Naphthalene Sequence

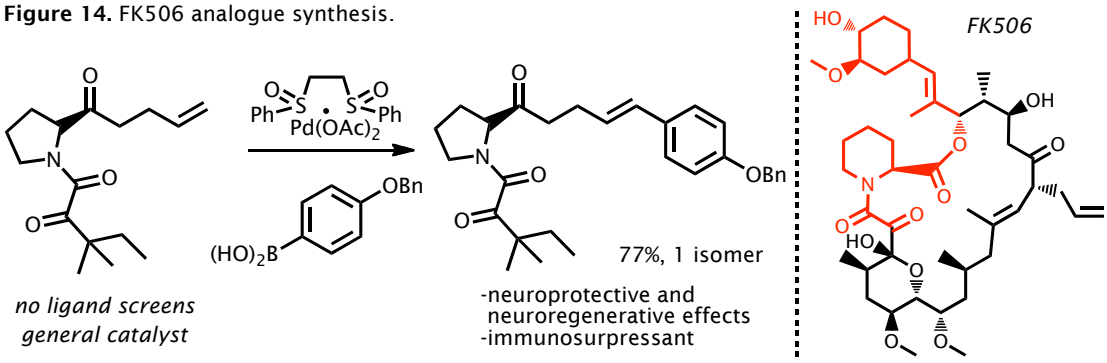


based transformations immediately following our reaction. These transition metal reaction sequences have the power to rapidly build complexity from simple starting materials.

2.2.3 Six-Member Chelators for Synthesis of Medicinally Relevant Intermediates

A number of synthetic advantages became evident when comparing the oxidative Heck arylation disconnect with common ways to construct bis-homoallylic substituted styrenyl molecules. Palladium (0) Heck arylation methods may be used to form FK506 segment anologues bearing bis-homoallylic functionality; however, phosphine ligand screening was necessary to achieve preparatively useful selectivities because the olefin isomers formed are not easily separable (figure 14).[16] Under our oxidative Heck

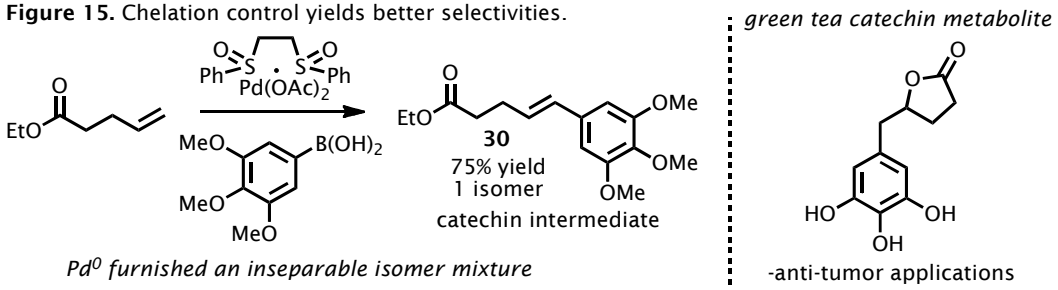
Figure 14. FK506 analogue synthesis.



conditions the desired coupling takes place with excellent regioselectivity of olefin isomers in preparative yields. The palladium (II)/bis-sulfoxide catalyst **1** has proven to be general with a broad range of substrates, which foregoes any need for catalyst or ligand screening.

A similar attempt to employ a palladium (0) based Heck reaction for the synthesis of the green tea catechin metabolite intermediate **30** failed due to the formation of a complex mixture of inseparable olefin isomers (figure 15).[17] Unfortunately, the direct

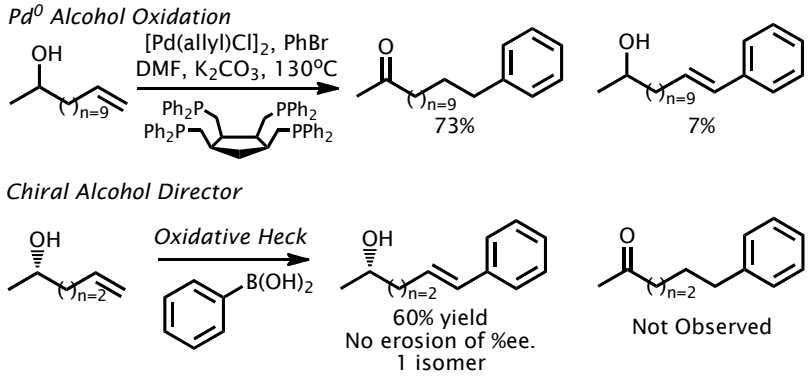
Figure 15. Chelation control yields better selectivities.



arylation route had to be abandon and replaced with a Claisen rearrangement route. This required the aryl motif to be incorporated in the starting material, thus preventing facile aryl diversification. However, under our oxidative Heck reaction conditions the bis-homoallylic ethyl ester couples smoothly to the electron-rich boronic acid in 75% yield. Significantly, the aryl moiety may be easily installed from a variety of commercial aryl boronic acids, allowing for rapid medicinal screening.

Bis-homoallylic alcohols are also excellent directors in this palladium (II) catalyzed reaction. Previously, alcohols with up to nine methylene spacers between the terminal olefin were often oxidized to the ketone during palladium (0) Heck arylations by double bond migration to form an enol, which readily tautomerizes to the ketone (figure 16).[18] The extensive double bond migration is due to a long-lived palladium hydride species capable of repeatedly inserting into the alkene. With the palladium (II)/

Figure 16. Pd^0 vs. Pd^{II} olefin-hydride isomerizations.

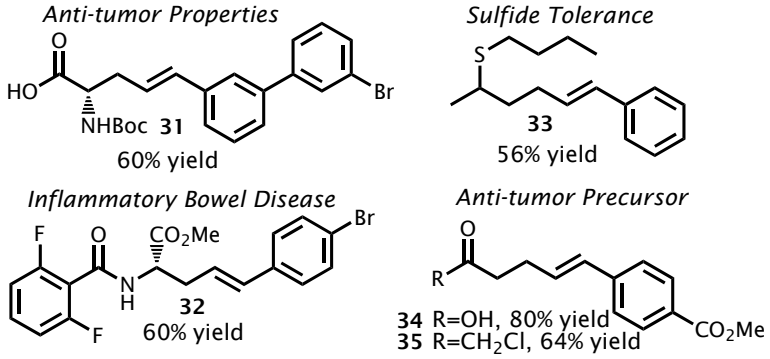


bis-sulfoxide catalyzed arylation conditions, bis-homoallylic alcohols are not oxidized and all chiral information is preserved. The lack of olefin isomerization indicates a short-lived palladium hydride species. The short-lived nature of this intermediate is likely due to two key differences in our catalytic system when compared to palladium (0) based Heck arylations: 1) the palladium hydrido acetate intermediate thermodynamically favors reductive elimination to form palladium (0) and acetic acid while the palladium hydrido halide intermediates formed in reductive Heck reactions favor the protonated palladium instead of palladium (0) and hydrohalic acid; 2) the reoxidation of palladium (0) with benzoquinone is a favorable process and further drives the equilibrium away from a hydrido palladium species. These two mechanistic differences allow chiral

alcohol substrates as seen in figure 16 to be compatible with our Heck-arylation conditions with no oxidation or erosion of optical purity.

Selective Heck arylations of amino acid derived pent-4-enoic acid **31** and pent-4-enoate **32** require different palladium (0) catalyst systems that must be empirically determined through extensive ligand and additive screens (figure 17).[19] In contrast, the

Figure 17. Medicinally relavent six-member chelators.



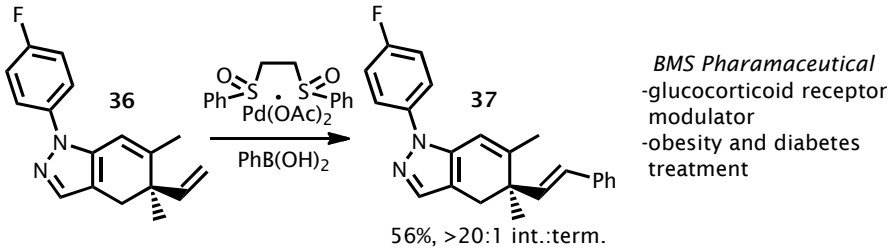
versatile palladium (II)/bis-sulfoxide catalyst **1** is general and furnishes a wide range of coupled products in good yields and outstanding selectivities. Significantly, aryl halide functionality is preserved throughout the course of the oxidative reaction. Each of the aryl halides in figure 17 were further elaborated via palladium (0) mediated Suzuki couplings.

Wittig olefination routes to isolated olefins with the straight chain bis-homoallylic carboxylic acid **34** and α-chloroketone **35** in figure 17 led to difficult to separate mixtures of *E:Z* olefins.[20] Under these mild oxidative Heck-arylation conditions, *E*-olefin products were formed exclusively for all substrates evaluated. Interestingly, bis-homoallylic thioether **33** couples smoothly. Thioethers are often incompatible moieties with palladium (II) mediated reactions due to catalyst binding, but the sulfur functionality serve as an excellent directing groups in this reaction.

2.2.4 Steric Directors and New Nucleophiles

During optimization and the testing of directing factors we found that substantial steric bulk adjacent to the olefin is tolerated in this Heck reaction without diminished reactivity. Even an α-olefin in close proximity to a quaternary center and near an exocyclic methyl group underwent oxidative Heck arylation to afford a BMS glucocorticoid receptor modulator **37** in preparative yields (figure 18).[21] Previously, this medicinally interesting molecule had been synthesized via a Wittig reaction as the final

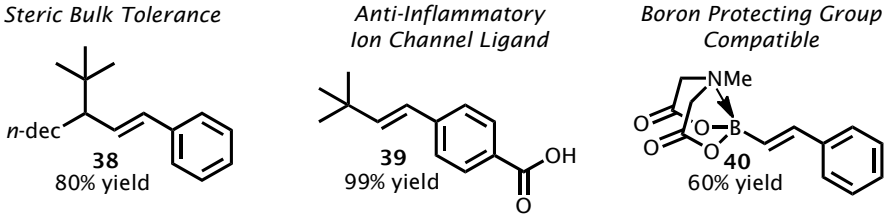
Figure 18. Oxidative Heck-arylation on a sterically encumbered olefin.



step to install the aryl ring. Our synthetic sequence proceeded through the same aldehyde intermediate to generate the terminal olefin **36** via the Wittig reaction, but we have the key benefit of a more readily substituted aryl moiety because currently >2200 aryl boronic acids and <200 benzylic Wittig reagents are commercially available.

Steric bulk was found to be universally tolerated and gave high selectivities for the arylated products (figure 19). Allylic *tert*-butyl hydrocarbon **38**, vinylic quarternary

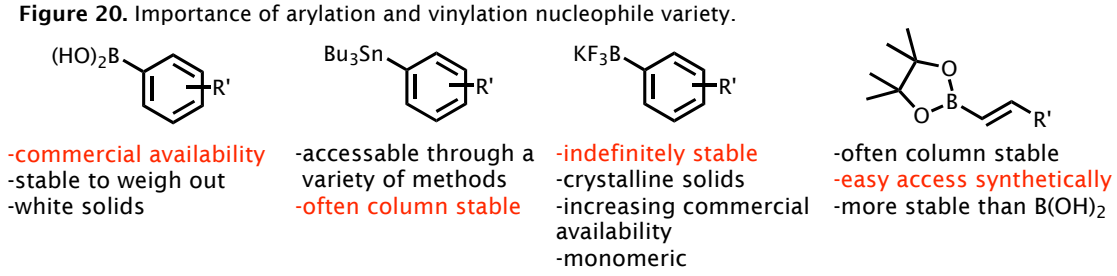
Figure 19. Steric directed arylation with a Pd^{II}/bisSO catalyst.



hydrocarbon **39** and vinylic protected tetrahedral boron **40** were all found to be good steric directors under our arylation conditions.[22] Importantly, the protected styrenyl boron is easily employed in palladium (0) coupling reactions after deprotection.

Synthetically, it is often beneficial to be able to access a variety of transmetalating agents to effect the same type of arylation since each nucleophile has different characteristics (figure 20). As previously mentioned, a vast number of aryl boronic acids

Figure 20. Importance of arylation and vinylation nucleophile variety.

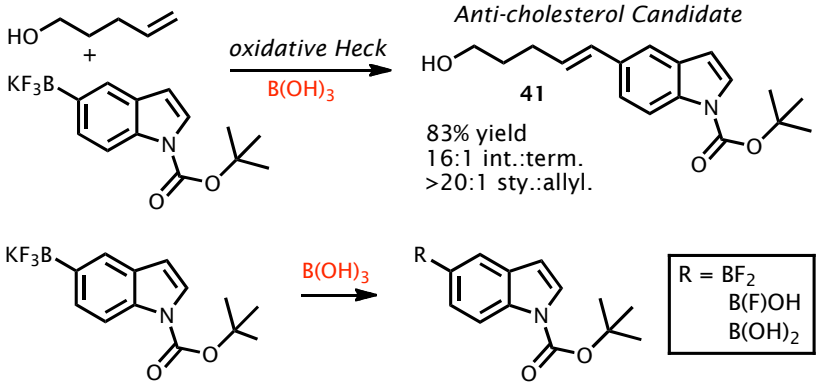


are commercially available, are often stable to air, and easy to weigh out; however, when synthesizing arylation compounds aryl tin reagents and potassium trifluoroborates have some advantages. Stannanes are available through a variety of reactions including nucleophilic displacements of tributyl stannyl halides and transition metal-based synthesis with stannyl dimers. The aryl tin products of these reactions are often column stable which allows for a simplified purification process. Both aryl tin reagents and aryl boronic acids work well under our oxidative Heck condition for allylic substituted terminal olefins substrates.

Potassium trifluoroborates are indefinitely stable crystalline solid compounds often isolated through simple filtration. Characterization of these compounds is frequently easier than their boronic acid counterparts since they are monomeric structures, whereas both the monomeric and trimeric forms of the aryl boronic acid are often present.[23] Potassium trifluoroborates are gaining increasing commercial support

largely due to these advantages. Under our palladium (II) catalyzed Heck reaction aryl BF_3K salts couple efficiently providing boric acid is added to the reaction mixture (figure 21). Their synthetic utility was demonstrated in accessing a patented anti-cholesterol

Figure 21. Potassium trifluoroborate nucleophile.

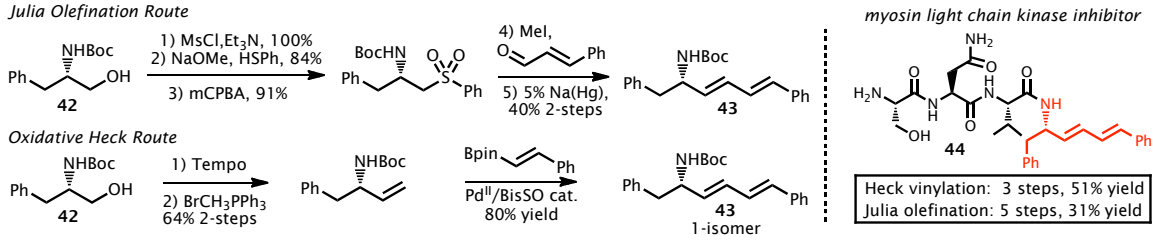


agent **41** where the potassium trifluoroborate was formed from the commercially available aryl pinacol boronic ester.[24] Under our reaction conditions aryl boronic esters transmetalate slowly and do not give preparatively useful yields; however, with a simple one-step conversion to corresponding aryl borate salt, the reaction proceeds smoothly with good yield and selectivities. The boric acid additive is likely a fluoride acceptor that opens a p-orbital on the aryl boron for transmetalation, since addition of boric acid to the BF_3K salt in an NMR tube rapidly converts the salt to the boronic acid and two other aryl species (presumably the mono- and difluorinated boron aryls). A similar observation was reported for the addition of TMSCl to BF_3K salts.[25]

Vinyl boronic esters are much more stable than their vinyl boronic acid counterparts, simple to access synthetically, and can often be isolated through column chromatography. Employment of vinyl boronic esters in our oxidative Heck manifold would allow for access to a new class of nucleophiles to complement an already broad substrate scope. While longer reaction times were necessary due to sluggish reactivity,

preparative yields and selectivities were observed for diene products at higher molarities providing the vinyl boronic ester is styrenyl. The arylated diene functionality proved to be valuable synthetically as a variety of medicinally interesting compounds posses this motif. Importantly, the oxidative Heck vinylation compares favorably with existing methodologies used to access these products. We directly compared our method to the olefination route employed for the synthesis of an intermediate to a myosin light chain kinase inhibitor **44** used for smooth muscle relaxation (figure 22).[26] The commonly used

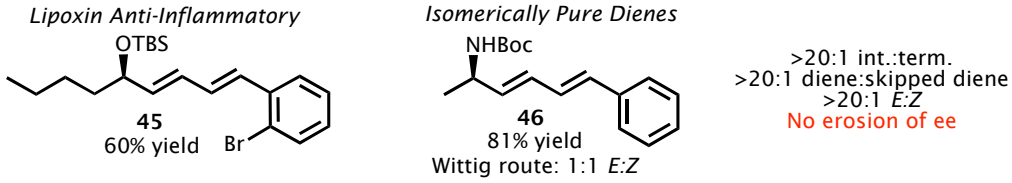
Figure 22. Synthetic comparison of a Julia olefination route to an oxidative Heck route.



Julia olefination route begins with *N*-Boc-protected phenyl alanol **42** and requires 5 steps to access the key arylated diene intermediate **43**. Beginning from the same amino alcohol **42**, only three steps were required to access the identical diene intermediate **43** as a single isomer in good yield with no erosion of optical purity. Significantly, an overall 20% boost in yield was observed for the oxidative Heck arylation route which requires minimal oxidation state changes and foregoes installation of an activating group that must be removed later.

Several other arylated dienes were synthesized in good yields as single isomers with no erosion of optical purity (figure 23). The allylic ether **45** was previously

Figure 23. Arylated diene synthesis in good selectivities and yields.



synthesized via a Suzuki coupling which required the selective oxidative addition of the palladium catalyst into a vinyl bromide bond over an aryl bromide bond. While the selective transformation was achieved in the synthesis of this potent anti-inflammatory lipoxin analogue, an oxidative Heck vinylation manifold forgoes all competing oxidative addition reactions and the aryl bromide is preserved throughout the reaction.[27]

Under the oxidative Heck vinylation conditions only the *E*-olefin isomer is observed likely due to our transformation occurring mildly at room temperature. Other olefination methods commonly used such as the Wittig olefination often erode *E:Z* ratios, as was the case for the chiral amine **46**. In contrast, the oxidative Heck reaction afforded a single isomer in good yields.

2.3 CONCLUSIONS

We have developed a general oxidative Heck reaction catalyzed by the versatile palladium (II)/bis-sulfoxide catalyst **1**, which proceeds with excellent selectivities for a broad range of non-resonance biased olefins. The catalyst is sensitive to chelation from proximal oxygen, nitrogen and sulfur moieties, steric encumbrance, and inductive direction. These directing events result in excellent regioselectivities for olefin insertion and β-hydride elimination for a variety of substrates. Palladium hydride isomerization of olefins is not observed under these mild, oxidative conditions as evidenced by excellent *E:Z* selectivities, no erosion in optical purity for proximal stereocenters, and a tolerance for unprotected alcohol moieties. We have significantly expanded the scope for the intermolecular Heck reaction with respect to terminal olefins and therefore have broadened its synthetic applications.

2.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents for the Heck arylation reaction were used as received: 1,4-benzoquinone and 2,6-dimethylbenzoquinone (Sigma-Aldrich); 5-bromoindole (Frontier Scientific Inc.); 4-methoxycarbonylphenylbornic acid, 2,5-difluorophenylboronic acid (Frontier Scientific Inc.); phenylboronic acid and 2-bromophenylboronic acid (Sigma-Aldrich); 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate "Catalyst **1**" (Sigma-Aldrich). Catalyst **1** was stored in a glove box under an argon atmosphere and weighed out in air prior to use. Solvents dioxane, tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N,N-dimethylformamide (DMF) (Sure Seal) was obtained from Sigma-Aldrich and used as received. All Heck arylation reactions were run under air with no precautions taken to exclude moisture. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate staining. Flash column chromatography was performed as described by Still using EM reagent silica gel 60 (230-240 mesh).[28] ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). ^{19}F NMR

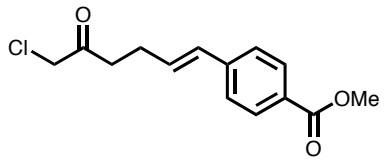
spectra were recorded on a Varian Unity-400 (376 MHz) or Varian-500 (470 MHz) spectrometer and are reported in ppm using a 1% $C_6F_6/CDCl_3$ standard referenced to -164.3 ppm. Regioselectivity of the Heck addition was determined by NMR analysis of the crude mixture. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were obtained using a JAS.CO DIP-370 digital polarimeter and a 3.5 x 100 mm cell.

General Procedure for Heck Arylation: To an 8 mL borosilicate vial were added sequentially: Catalyst **1** (10 mol%, 0.1 mmol), benzoquinone (2 equiv, 2 mmol), dioxane (0.33M, 3 mL), acetic acid (4 equiv, 4 mmol), olefin (1 equiv., 1 mmol), boronic acid (1.5 equiv., 1.5 mmol), and a stir bar. The vial was capped and stirred at room temperature with the reaction progress monitored by TLC or NMR aliquot (4hrs). The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 or hexane (2 times). The combined organics were dried over $MgSO_4$. The mixture was filtered and concentrated *in vacuo*. Purification by flash chromatography (EtOAc/hexanes mixtures) provided the pure product.

The only deviation from standard conditions have been increasing aryl boronic acids loadings for compounds **2, 3, 5,** and **14**. Increasing aryl boronic acids loading (from 1.5 to 2.0 equiv.) was found to improve internal:terminal product ratios due to further arylation of the minor terminal product to generate trisubstituted olefins. Increasing

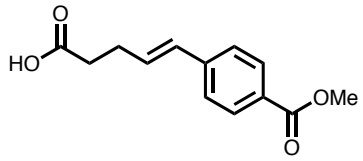
reaction times (from 4hrs to 24hrs) for compound **5, 6, 7, 9,** and **10** (48h) was found to give better styrenyl:allylic ratios due to erosion of the minor allylic isomer.

Diene Formation Conditions: Following the General Procedure with 2 equiv. 2,6-dimethylbenzoquinone, 1.0 M dioxane, and reaction time of 48 hours. Drastically diminished yields are observed when benzoquinone is used, which was determined to be due to Diels-Alder reactions with the diene products and benzoquinone.



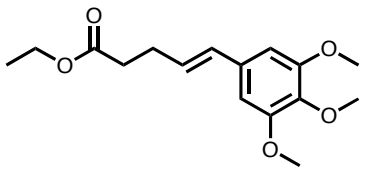
(*E*)-methyl 4-(6-chloro-5-oxohex-1-enyl)benzoate: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), 1-chlorohex-5-en-2-one (1.0 mmol, 133.0 mg, 1 equiv.), 4-methoxycarbonylphenylboronic acid (2.0 mmol, 360.0 mg, 2.0 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15% ethyl acetate/hexanes then further purified via silica chromatography (125 mL SiO_2) with 100% methylene chloride as eluent to yield (*E*)-methyl 4-(6-chloro-5-oxohex-1-enyl)benzoate as a white solid. Run 1 (172.7 mg, 0.65 mmol, 65%, >20:1 *E:Z*, 16:1 int.:term., >20:1 int.:allyl, 13:1 styrenyl:diene); run 2 (166.6 mg, 0.62 mmol, 62%, >20:1 *E:Z*, 16:1 int.:term., >20:1 styrenyl:allyl, 13:1

styrenyl:diene). **Average Yield = 64%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 16 Hz, 1H), 6.32 (dt, *J* = 16, 6.4 Hz, 1H), 4.10 (s, 2H), 3.90 (s, 3H), 2.81 (t, 6.8 Hz, 2H), 2.56 (ap q, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 202.01, 167.12, 141.85, 131.16, 130.72, 130.12, 128.88, 126.13, 52.28, 48.40, 39.22, 27.06. IR (neat, cm^{-1}) 3011.79, 2991.84, 2947.42, 2910.79, 1725.83, 1716.12. HRMS (ESI) *m/z* calculated for $C_{14}H_{16}O_3Cl$ $[M+H]^+$: 267.0788, found 267.0795. It is known the Pd(II) and benzoquinone can convert carbonyl compounds to α,β-unsaturated carbonyls.[29]



(*E*)-5-(4-(methoxycarbonyl)phenyl)pent-4-enoic acid: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), 4-pentenoic acid (1.0 mmol, 100.0 mg, 1 equiv.), 4-methoxycarbonylphenylboronic acid (2.0 mmol, 360.0 mg, 2.0 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with methylene chloride (50 ml) and rinsed with 10% aq. H_3PO_4 (50 ml). The aqueous layer was extracted with methylene chloride (50 ml) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% acetone/hexanes as eluent to yield (*E*)-5-(4-(methoxycarbonyl)phenyl)pent-4-enoic acid as a white solid. Run 1 (184.9 mg, 0.79 mmol, 79%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (187.7 mg, 0.80 mmol, 80%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average Yield = 80%.** ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 16 Hz, 1H), 6.34 (m, 1H), 3.90 (s, 3H), 2.56 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.74, 167.18, 141.92, 131.12, 130.63, 130.12, 128.85, 126.16, 52.29, 33.62, 28.15. IR (neat, cm^{-1}) 3119.86, 3010.62, 2926.10, 1719.65, 1693.39. HRMS (ESI) *m/z* calculated for $C_{13}H_{14}O_4Na$ $[M+Na]^+$: 257.0790, found 257.0783. Spectra taken in d_6-DMSO matches reported assignments.[30]



(*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate: To a 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.1 mg, 10 mol%), benzoquinone (1 mmol, 108.0 mg, 2 equiv.), dioxane (1.5 mL, 0.33 M), acetic acid (2.0 mmol, 120.0 mg, 4 equiv.), ethyl pent-4-enoate (0.5 mmol, 64.0 mg, 1 equiv.), 3,4,5-trimethoxyphenylboronic acid (0.75 mmol, 127.3 mg, 1.2 equiv.), and a stir bar sequentially under ambient conditions. The vial was capped and stirred at 45°C for 4 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate as a white solid. Run 1 (111.5 mg, 0.38 mmol, 75%, >20:1 *E:Z*, 8:1 int.:term., >20:1 sty.:allyl.); run 2 (108.8, 0.37 mmol, 74%, >20:1 *E:Z*, 8:1 int.:term., >20:1 sty.:allyl.). **Average Yield = 75%.** ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.12 (dt, *J* = 15.6, 6.8 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 2.55-2.45 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.22, 153.48, 137.58, 133.40, 131.07,

128.29, 103.19, 61.16, 60.66, 56.25, 34.25, 28.42, 14.50. IR (neat, cm^{-1}) 2979.87, 2938.51, 2837.43, 1730.54. HRMS (ESI) *m/z* calculated for $C_{16}H_{23}O_5$ $[M+H]^+$: 295.1545, found 295.1537. A known compound however no spectral data is reported.[31]

Alternative Oxidants:

Oxygen:

(*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate: To a 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.1 mg, 10 mol%), dioxane (1.5 mL, 0.33 M), acetic acid (2.0 mmol, 120.0 mg, 4 equiv.), ethyl pent-4-enoate (0.5 mmol, 64.0 mg, 1 equiv.), 3,4,5-trimethoxyphenylboronic acid (0.75 mmol, 127.3 mg, 1.5 equiv.), an oxygen balloon, and a stir bar sequentially under ambient conditions. Nitrobenzene was added as an internal standard. The vial was capped and stirred at 45ºC for 4 hours. GC analysis revealed a 11% conversion with a 5% yield of (*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate (response factor corrected).

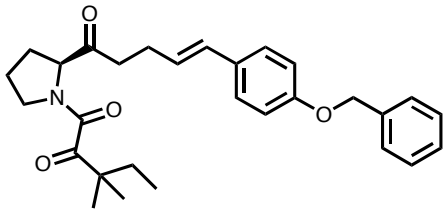
Air:

Replacing the oxygen balloon with an air balloon in the above procedure yielded a 10% conversion with a 4% yield of (*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate (response factor corrected).

Hydrogen Peroxide:

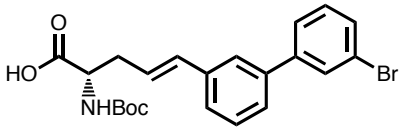
(*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate: To a 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.1 mg, 10 mol%), dioxane (1.5 mL, 0.33 M), acetic acid

(2.0 mmol, 120.0 mg, 4 equiv.), hydrogen peroxide (1.0 mmol, 68 μL, 2 equiv., 50% aq. solution), ethyl pent-4-enoate (0.5 mmol, 64.0 mg, 1 equiv.), 3,4,5-trimethoxyphenylboronic acid (0.75 mmol, 127.3 mg, 1.5 equiv.), and a stir bar sequentially under ambient conditions. Nitrobenzene was added as an internal standard. The vial was capped and stirred at 45ºC for 4 hours. GC analysis revealed a 100% conversion with a 6% yield of (*E*)-ethyl 5-(3,4,5-trimethoxyphenyl)pent-4-enoate (response factor corrected).



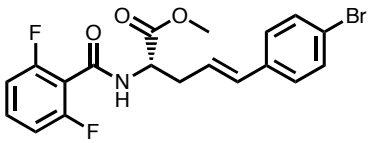
(*S*,*E*)-1-(2-(5-(4-(benzyloxy)phenyl)pent-4-enoyl)pyrrolidin-1-yl)-3,3-dimethylpentane-1,2-dione: To a 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.1 mg, 10 mol%), benzoquinone (1.0 mmol, 108.0 mg, 2 equiv.), dioxane (1.5 mL, .33 M), acetic acid (2.0 mmol, 120.0 mg, 4 equiv.), (*S*)-3,3-dimethyl-1-(2-pent-4-enoylpyrrolidin-1-yl)pentane-1,2-dione (0.5 mmol, 139.5 mg, 1 equiv. derived from *N*-(*tert*-Butoxycarbonyl)-L-proline *N*'-methoxy-*N*'-methylamide), 4-(benzyloxy)phenylboronic acid (1.0 mmol, 228.1 mg, 2.0 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 24 hours. The mixture was diluted with methylene chloride (50 mL) and rinsed with 5% K_2CO_3 (50 ml). The aqueous layer was extracted with methylene chloride (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20 % ethyl acetate/petroleum ether as eluent to yield (*S*,*E*)-1-(2-(5-(4-(benzyloxy)phenyl)pent-4-enoyl)pyrrolidin-1-yl)-3,3-dimethylpentane-1,2-dione as a white solid. Run 1 (177.7 mg,

0.39 mmol, 77%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (175.4 mg, 0.38 mmol, 77%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average yield = 77%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.36 (d, *J* = 15.5 Hz, 1H), 6.05 (dt, *J* = 16.0, 7.0 Hz, 1H), 5.05 (s, 2H), 4.61 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.57 – 3.45 (m, 2H), 2.80 – 2.65 (m, 2H), 2.54 – 2.46 (m, 2H), 2.20 – 2.13 (m, 1H), 1.98 – 1.76 (m, 4H), 1.71 – 1.63 (m, 1H), 1.25 (s, 3H), 1.21 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H), minor rotamer: 4.74 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.67 – 3.64 (m, 2H), 2.33-2.26 (m, 1H), 1.29 (s, 3H), 1.14 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.04, 165.28, 158.20, 137.16, 130.69, 130.62, 130.43, 128.95(rotamer), 128.78, 128.16, 127.67, 127.33, 126.77, 126.54(rotamer), 115.34(rotamer), 115.05, 70.19, 66.01(rotamer), 64.21, 47.64, 47.20, 47.13(rotamer), 40.06, 39.40(rotamer), 33.11(rotamer), 32.50, 30.75(rotamer), 27.88, 26.81, 24.98, 24.23(rotamer), 24.00, 23.28, 22.28(rotamers), 9.17. IR (neat, cm^{-1}): 3030.11, 2964.43, 2923.88, 2879.91, 1721.50, 1699.12, 1634.63, 1606.08, 1508.52. HRMS (ES) *m/z* calculated for $C_{29}H_{36}NO_4$ $[M+H]^+$: 462.2644, found 462.2649. $[\alpha]^{25}_D$ = -37.1 (c = 1.0, $CHCl_3$). Spectral data matches reported assignments.[32]



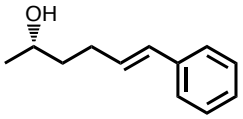
(*S*,*E*)-2-(*tert*-butoxycarbonyl)-5-(3-[3-bromobenzene]phenyl)pent-4-enoic acid: To a 2 mL borosilicate vial was added catalyst **1** (0.022 mmol, 11.0 mg, 10 mol%), benzoquinone (0.44 mmol, 47.5 mg, 2 equiv.), dioxane (0.66 mL, .33 M), acetic acid (0.88 mmol, 52.8 mL, 4 equiv.), (*S*)-2-(*tert*-butoxycarbonyl)pent-4-enoic acid (0.22 mmol, 47.3 mg, 1

equiv., derived from L-allylglycine), 3-(3-bromobenzene)phenyl boronic acid (0.327 mmol, 90.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 24 hours. The mixture was diluted with ether (50 mL) and rinsed with 1 M H_3PO_4 (50 ml). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 30% ethyl acetate/petroleum ether/1% acetic acid as eluent to yield (*S*,*E*)-2-(*tert*-butoxycarbonyl)-5-(3-[3-bromobenzene]phenyl)pent-4-enoic acid as a white solid. Run 1 (58.9 mg, 0.13 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (59.9, 0.13 mmol, 61%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average yield = 61%.** ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.72 (s, 1H), 7.50-7.47 (m, 3H), 7.42-7.36 (m, 3H), 7.30 (t, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 15.5 Hz, 1H), 6.19 (dt, *J* = 15.5, 7.5 Hz, 1H), 5.05 (d, *J* = 7.0 Hz, 1H), 4.48 (m, 1H), 2.81-2.70 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CHCl_3$) δ 176.99, 155.78, 143.39, 140.30, 137.68, 134.15, 130.51 (2 C), 130.42, 129.34, 126.60, 126.04, 125.99, 125.42, 124.55, 123.13, 80.71, 53.29, 36.10, 28.54. IR (neat, cm^{-1}): 3426.17, 3115.84, 2975.37, 2530.59, 1713.05. HRMS (ESI) *m/z* calculated for $C_{22}H_{25}NO_4Br$ $[M+H]^+$: 446.0967, found 446.0969. $[\alpha]^{27}_D$ = +9.1° (c = 0.44, $CHCl_3$). A known compound however no spectral data is reported.[33]

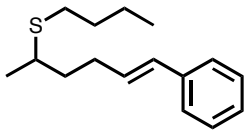


(*S*,*E*)-methyl 5-(4-bromophenyl)-2-(2,6-difluorobenzamido)pent-4-enoate: To a 2 mL borosilicate vial was added catalyst **1** (0.025 mmol, 12.5 mg, 10 mol%), benzoquinone (0.5 mmol, 54.0 mg, 2 equiv.), dioxane (0.75 mL, .33 M), acetic acid (1.0 mmol, 60.0

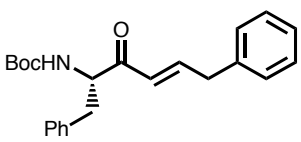
mg, 4 equiv.), (*S*)-methyl 2-(2,6-difluorobenzamido)pent-4-enoate (0.25 mmol, 67.3 mg, 1 equiv., derived from L-allylglycine), 4-bromophenylboronic acid (0.375 mmol, 74.6 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 24 hours. The mixture was diluted with ether (50 mL) and rinsed with H_2O (50 ml). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 35% ethyl acetate/petroleum ether as eluent to yield (*S,E*)-methyl 5-(4-bromophenyl)-2-(2,6-difluorobenzamido)pent-4-enoate as a white solid. Run 1 (63.3 mg, 0.15 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (65.1 mg, 0.15 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average yield = 60%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.38 (m, 1H), 7.20 (d, J = 8.5 Hz, 2H), 6.95 (t, J = 8.0 Hz, 2H), 6.61 (br d, J = 7.0 Hz, 1H), 6.45 (d, J = 15.5 Hz, 1H), 6.09 (dt, J = 16.0, 7.0 Hz, 1H), 5.00 (q, J = 7.5, 1H), 3.81 (s, 3H), 2.94 (m, 1H), 2.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.79, 160.27 (dd, J^1 ^{19}F-^{13}C = 251.1, 6.8 Hz, 1C), 160.06, 135.96, 133.59, 132.24 (t, J^3 ^{19}F-^{13}C = 9.9 Hz, 1C), 131.84, 128.04, 124.11, 121.55, 113.89 (t, J^2 ^{19}F-^{13}C = 19.5 Hz, 1C), 112.31 (d, J^2 ^{19}F-^{13}C = 25.8 Hz, 1C), 52.97, 52.65, 35.95. ^{19}F (376 MHz, $CDCl_3$) -112.36. IR (neat, cm^{-1}) 3336.51, 3272.50, 3081.23, 3060.90, 2967.34, 2924.14, 1743.88, 1676.48, 1514.27, 1223.17. HRMS (ESI) *m/z* calculated for $C_{19}H_{17}NO_3F_2Br$ $[M+H]^+$: 424.0360, found 424.0354. $[\alpha]^{27}_D$ = +44.2° (c = 0.44, $CHCl_3$). A known compound however spectral data is not reported.[34]



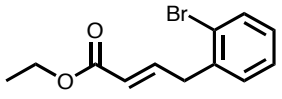
(*S*,*E*)-6-phenylhex-5-en-2-ol: To a 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3.0 mL, .33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), *S*-(+)-2-hexenol (1.0 mmol, 100.0 mg, 1 equiv.), phenylboronic acid (1.5 mmol, 183.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 2.5 hours. The mixture was diluted with methylene chloride (50 mL) and rinsed with 3M NaOH (50 ml). The aqueous layer was extracted with methylene chloride (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20 % ether:pentroleum ether as eluent to yield (E)-6-phenylhex-5-en-2-ol as white solid. Run 1 (107.6 mg, 0.61 mmol, 61%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (105.8 mg, 0.60 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average yield = 61%** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.24 (dt, *J* = 15.6, 6.8 Hz, 1H), 3.88 (sex, *J* = 6.4 Hz, 1H), 2.40-2.24 (m, 2H), 1.70–1.57 (m, 2H), 1.39 (br s, 1H), 1.23 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.57, 130.52, 128.78, 127.23, 126.23 (2C), 67.93, 39.01, 29.66, 23.87. IR (neat, cm^{-1}): 3645.89-3151.87, 3079.26, 3057.15, 3023.31, 2963.55, 2926.95, 2871.97, 2853.80, 1648.31, 1596.93. HRMS (CI) *m/z* calculated for $C_{12}H_{17}O$ $[M+H]^+$: 177.1280, found 177.1277. $[\alpha]^{25}_D$ = +12.4° (c = 1.0, $CHCl_3$). Spectral peaks are similar to reported peaks (spectrum reported in CCl_4).[35]



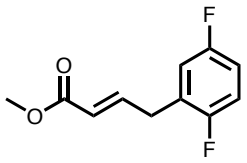
(*E*)-butyl (6-phenylhex-5-en-2-yl)sulfane: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3.0 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), butyl (hex-5-en-2-yl)sulfane (1.0 mmol, 170.0 mg, 1 equiv.), phenylboronic acid (1.5 mmol, 183.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 24 hours. The mixture was diluted with methylene chloride (50 mL) and rinsed with H_2O (50 ml). The aqueous layer was extracted with methylene chloride (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 5 % ether/petroleum ether as eluent to yield (E)-butyl (6-phenylhex-5-en-2-yl)sulfane as light yellow oil. Run 1 (138.0 mg, 0.56 mmol, 55%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.); run 2 (138.0 mg, 0.56 mmol, 56%, >20:1 *E:Z*, >20:1 int.:term., >20:1 sty.:allyl.). **Average yield = 56%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.20 (dt, *J* = 15.5, 7.0 Hz, 1H), 2.79 (sex., *J* = 7.0 Hz, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.35 (m, 2H), 1.73 (m, 1H), 1.64 (m, 1H), 1.56 (q, *J* = 8.0 Hz, 2H), 1.41 (m, 2H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.90, 130.50, 130.31, 128.71, 127.13, 126.13, 39.53, 36.69, 32.20, 30.66, 30.16, 22.39, 21.69, 13.96. IR (neat, cm^{-1}) 3059.47, 3023.77, 2956.85, 2926.52, 2870.53, 2858.22. HRMS (ESI) *m/z* calculated for $C_{16}H_{25}S$ $[M+H]^+$: 249.1677, found 249.1687.



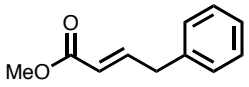
(*S*,*E*)-*tert*-butyl 3-oxo-1,6-diphenylhex-4-en-2-ylcarbamate: To an 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%), benzoquinone (1.0 mmol, 108.0 mg, 2 equiv.), dioxane (1.5 mL, .33 M), acetic acid (2.0 mmol, 120.0 mg, 4 equiv.), (S)-tert-butyl 3-oxo-1-phenylhex-5-en-2-ylcarbamate (0.5 mmol, 144.5 mg, 1 equiv., derived from *N*-Boc-L-phenylalanine), phenylboronic acid (0.75 mmol, 92.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at 45ºC for 48 hours. The mixture was diluted with ether (50 mL) and rinsed with H_2O (50 ml). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO2) with 20% ethyl acetate/petroleum ether as eluent to yield (*S*,*E*)-*tert*-butyl 3-oxo-1,6-diphenylhex-4-en-2-ylcarbamate as a clear solid. Run 1 (111.8 mg, 0.31 mmol, 61%, >20:1 *E:Z*, >20:1 int.:term., <1:20 sty.:allyl.); run 2 (113.3 mg, 0.31 mmol, 62%, >20:1 *E:Z*, >20:1 int.:term., <1:20 sty.:allyl.). **Average yield = 62%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5, 2H), 7.27-7.20 (m, 4H), 7.10 (ap t, *J* = 6.5 Hz, 4H), 7.03 (dt, *J* = 15.5, 6.5 Hz, 1H), 6.09 (d, *J* = 16.0 Hz, 1H), 5.26 (d, *J* = 7.5 Hz, 1H), 4.79 (ap q, *J* = 6.5 Hz, 1H), 3.49 (d, *J* = 7.0 Hz, 2H), 3.07 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.98 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.69, 155.32, 147.94, 137.41, 136.30, 129.68, 129.03, 128.97, 128.64, 128.15, 127.08, 127.02, 79.90, 58.57, 39.04, 38.70, 28.49. IR (neat, cm^{-1}) 3420.31, 3346.22, 3085.09, 3061.84, 3027.95, 2976.31, 2929.68, 1711.23, 1692.91. HRMS (ESI) *m/z* calculated for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2069, found 366.2068. $[\alpha]^{27}_D$ = +51.3º (c = 1.0, $CHCl_3$), -5.6º (c = 1.0, MeOH). Spectral data matches that of the reported compound.[36]



(*E*)-ethyl 4-(2-bromophenyl)but-2-enoate: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3.0 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), ethyl but-1-enoate (1.0 mmol, 114.0 mg, 1 equiv.), 2-bromobenzeneboronic acid (1.5 mmol, 300.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with Et_2O (50 ml) and rinsed with H_2O (50 mL). The aqueous layer was extracted with Et_2O (50 ml) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15% diethyl ether/pentane as eluent to yield (*E*)-ethyl 4-(2-bromophenyl)but-2-enoate as a clear oil. Run 1 (131.8 mg, 0.49 mmol, 49%, >20:1 *E:Z*, >20:1 int.:term., 1:20 sty.:allyl); run 2 (134.5 mg, 0.50 mmol, 50%, >20:1 *E:Z*, >20:1 int.:term., 1:17 sty.:allyl); run 3 (137.2 mg, 0.51 mmol, 51%, >20:1 *E:Z*, >20:1 int.:term., 1:19 sty.:allyl). **Average Yield = 50%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8 Hz, 1H), 7.28 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.09 (dt, *J* = 15.5, 7 Hz, 1H), 5.79 (d, *J* = 16 Hz, 1H), 4.20 (q, *J* = 7.5 Hz, 2H), 3.68 (d, *J* = 6.5 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.62, 145.64, 137.57, 133.21, 130.97, 128.70, 127.94, 124.81, 123.10, 60.56, 38.79, 14.45. IR (neat, cm^{-1}) 3.055.85, 2979.23, 2935.80, 2903.09, 1717.18. HRMS (ESI) *m/z* calculated for $C_{12}H_{14}O_2Br$ $[M+H]^+$: 269.0177, found 269.0172. Spectral data matches that of the reported compound.[37]

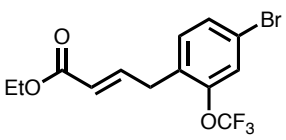


(*E*)-methyl 4-(2,5-difluorophenyl)but-2-enoate: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), methyl but-3-enoate (1.0 mmol, 100.0 mg, 1 equiv.), 2,5-difluorophenylboronic acid (1.5 mmol, 237.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with Et_2O (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with Et_2O (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15% ether/pentane as eluent to yield (*E*)-methyl 4-(2,5-difluorophenyl)but-2-enoate as a clear oil. Run 1 (110.0 mg, 0.52 mmol, 52%, >20:1 *E:Z*, >20:1 int.:term., 1:17 sty.:allyl.); run 2 (106.6 mg, 0.50 mmol, 50%, >20:1 *E:Z*, >20:1 int.:term., 1:17 sty.:allyl.). **Average Yield = 51%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08-6.99 (m, 2H), 6.94-6.86 (m, 2H), 5.83 (d, *J* = 15.5 Hz, 1H), 3.74 (s, 3H), 3.53 (d, *J* = 6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.81, 145.13, 122.99, 117.41 (d, *J* = 4.9 Hz), 117.22 (d, *J* = 4.9 Hz), 116.78 (d, *J* = 7.8 Hz), 116.58 (d, *J* = 8.8 Hz), 115.22 (d, *J* = 8.8 Hz), 115.04 (d, *J* = 8.8 Hz), 51.79, 31.68. ^{19}F NMR (470 MHz, $CDCl_3$) δ -119.27, -124.52. IR (neat, cm^{-1}) 3036.60, 2995.61, 2953.20, 2851.99, 1724.78. HRMS (ESI) *m/z* calculated for $C_{11}H_{11}O_2F_2$ $[M+H]^+$: 213.0727, found 213.0723. Previously reported compound however no spectral data is reported.[38]



(*E*)-methyl 4-phenylbut-2-enoate and (*E*)-methyl 4-phenylbut-3-enoate: To an 8 mL borosilicate vial was added White Catalyst (0.1

mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), methyl but-3-enoate (1.0 mmol, 102.0 mg, 1 equiv.), phenylboronic acid (1.5 mmol, 183.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial as capped and stirred at room temperature for 4 hours. The mixture was diluted with diethyl ether (50 mL) and rinsed with 5% K_2CO_3 (50 ml). The aqueous layer was extracted with diethyl ether (50 mL) and the combined organic layers were dried over $MgSO_4$. The crude product was purified via silica chromatography (125 mL SiO_2) with 10% diethyl ether/petroleum ether as eluent to yield (*E*)-methyl 4-phenylbut-2-enoate and (*E*)-methyl 4-phenylbut-3-enoate as a clear oil (125.0 mg, 0.71 mmol, 71%, >20:1 *E:Z*, 1:4 styrenyl:α,β-unsaturation). Silica gel chromatography was performed with liberal fraction collection. Crude product ratios are close to those of the purified material. ^{1}H NMR (500 MHz, $CDCl_3$) δ α,β-unsaturated: 7.12 (dt, *J* = 15.5, 6.0 Hz, 1H), 5.83 (d, *J* = 15.0 Hz, 1H), 3.73 (s, 3H), 3.54 (d, *J* = 6.5 Hz, 2H). Styrene: 6.51 (d, *J* = 15.5 Hz, 1H), 6.31 (dt, *J* = 15.5, 6.5 Hz, 1H), 3.27 (d, *J* = 7.5 Hz, 2H).



(*E*)-ethyl 4-(4-bromo-2-(trifluoromethoxy))phenyl)but-2-enoate: To a 4 mL borosilicate vial was added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%), benzoquinone (1.0 mmol, 108.0 mg, 2 equiv.), THF (1.5 mL, .33 M), acetic acid (2.0 mmol, 120.0 mg, 4 equiv.), ethyl but-3-enoate (0.5 mmol, 57.0 mg, 1 equiv.), 4-bromo-2-(trifluoromethoxy)phenylboronic acid (0.75 mmol, 213.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions.

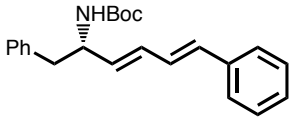
The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with ether (50 mL) and rinsed with H_2O (50 ml). The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 10% ether/petroleum ether as eluent to yield (E)-ethyl 4-(4-bromo-2-(trifluoromethoxy))phenyl)but-2-enoate as a yellow oil. Run 1 (159.1 mg, 0.3 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., <1:20 sty.:allyl.); run 2 (105.9 mg, 0.3 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term., <1:20 sty.:allyl.). **Average yield = 60%.** ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.42 (t, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.98 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.78, (dt, *J* = 15.5, 1.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.52 (dd, *J* = 6.5, 1.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.34, 144.67, 132.37, 130.50, 129.76, 124.30, 124.28, 123.55, 121.89, 121.06, 60.68, 32.18, 14.43. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.67. IR (neat, cm^{-1}) 3051.79, 2980.89, 2960.98, 2934.69, 2908.87, 2873.52, 1721.71, 1255.02, 1214.04, 1175.50. HRMS (ESI) *m/z* calculated for $C_{13}H_{13}O_3F_3Br$ $[M+H]^+$: 353.0000, found 353.0004. Previously reported compound.[39]

(E)-methyl 6-phenylhex-5-enoate (and other isomers): To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), methyl hex-5-enoate (1.0 mmol, 128.0 mg, 1 equiv.), phenylboronic acid (2.0 mmol, 244.0 mg, 2.0 equiv.) and a stir bar sequentially under ambient conditions. The vial as capped and stirred at room temperature for 24 hours. The mixture was diluted with diethyl ether (50

mL) and rinsed with 5% K_2CO_3 (50 ml). The crude product was purified via silica chromatography (125 mL SiO_2) with 5 % ether:petroleum ether as eluent to yield (E)-methyl 6-phenylhex-5-enoate and other isomers as clear oil. Silica gel chromatography was performed with liberal fraction collection. Crude product ratios match those of the purified material. *E:Z* selectivities were found to be >20:1 in all cases. Run 1 (124.4 mg, 0.61 mmol, 61%, internal:terminal 9:1, styrenyl:allylic 2:1); run 2 (120.4 mg, 0.59 mmol, 59%, internal:terminal 9:1, styrenyl:allylic 2:1). **Average yield = 60%.** ^{1}H NMR (500 MHz, $CHCl_3$) δ Styrenyl: 6.42 (d, *J* = 16 Hz, 1H), 6.20 (dt, *J* = 16, 6.5 Hz, 1H) Allylic: 5.68-5.62 (m, 1H), 5.56-5.50 (m, 1H) Terminal: 5.31 (d, *J* = 1.5 Hz), 5.09 (d, *J* = 1.5 Hz, 1H).

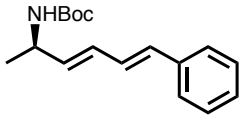
(*E*)-1-(undec-1-enyl)benzene (and other olefin isomers): To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), 1-undecene (1.0 mmol, 154.0 mg, 1 equiv.), phenylboronic acid (1.5 mmol, 183.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial as capped and stirred at room temperature for 4 hours. The mixture was diluted with diethyl ether (50 mL) and rinsed with 5% K_2CO_3 (50 ml). The aqueous layer was extracted with diethyl ether (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 100% petroleum ether as eluent to yield (*E*)-1-(undec-1-enyl)benzene and other olefin isomers as a clear oil. Silica gel chromatography was performed with liberal fraction collection. Crude product ratios match those of the purified material. *E:Z*

selectivities were found to be >20:1 in all cases. Run 1 (0.154 g, 0.67 mmol, 67%, internal:terminal 8:1, styrenyl:allylic 1:1), run 2 (0.156 g, 0.68 mmol, 68%, internal:terminal 8:1, styrenyl:allylic 1:1). **Average yield = 68%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ Styrenyl: 6.43 (d, *J* = 15.6 Hz, 1H), 6.28 (dt, *J* = 16, 6.8 Hz, 1H). Allylic: 5.66-5.52 (m, 2H), 3.38 (d, *J* = 6 Hz, 2H). Terminal: 5.31 (s, 1H), 5.10 (s, 1H), 2.55 (t, *J* = 6.8 Hz, 2H).



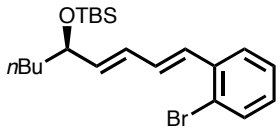
***tert*-butyl (*S*,3*E*,5*E*)-1,6-diphenylhexa-3,5-dien-2-ylcarbamate:** To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), 2,6-dimethylbenzoquinone (2.0 mmol, 272.0 mg, 2 equiv.), dioxane (1 mL, 1.0 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), (*S*)-*tert*-butyl 1-phenylbut-3-en-2-ylcarbamate (1.0 mmol, 248.0 mg, 1 equiv., derived from L-phenylalanol), (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (1.5 mmol, 348.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 48 hours. The mixture was diluted with ethyl acetate (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with ethyl acetate (50 ml) and the combined organic layers were thoroughly rinsed with 5% aq. K_2CO_3 and sat. aq. $NaHSO_3$ (Careful! Rapid Gas Evolution!) then dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 5% ethyl acetate/hexanes as eluent to yield *tert*-butyl (*S*,3*E*,5*E*)-1,6-diphenylhexa-3,5-dien-2-ylcarbamate as a white solid. Run 1 (283.5 mg, 0.81 mmol, 81%, >20:1 *E:Z*, >20:1 int.:term.); run 2 (277.9 mg, 0.75 mmol, 75%, >20:1 *E:Z*, >20:1 int.:term.). **Average Yield = 80%**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J*

= 8 Hz, 4H), 7.23 (m, 4H), 6.75 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.52 (d, *J* = 15.5 Hz, 1H), 6.29 (dd, *J* = 15, 10.5 Hz, 1H), 5.77 (m, 1H), 4.55 (br s, 2H), 2.91 (br s, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 155.35, 137.55, 137.39, 133.95, 132.60, 130.86, 129.80, 128.81, 128.60, 128.43, 127.73, 126.73, 126.53, 79.69, 53.16, 41.98, 28.55. IR (neat, cm^{-1}) 3079.13, 3059.71, 3027.59, 2979.74, 2929.05, 1699.26. HRMS (ESI) *m/z* calculated for $C_{23}H_{28}O_2N$ $[M+H]^+$: 350.2120, found 350.2121. $[\alpha]^{27}_D$ = -21.3° (c = 1.0, $CHCl_3$). Spectral data matches that of the reported compound.[40]



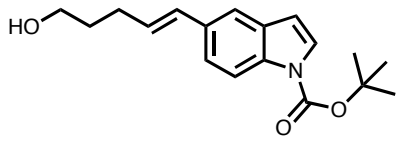
***tert*-butyl (*R*,3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ylcarbamate:** To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), 2,6-dimethylbenzoquinone (2.0 mmol, 272.0 mg, 2 equiv.), dioxane (1 mL, 1.0 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), (*R*)-*tert*-butyl but-3-en-2-ylcarbamate (1.0 mmol, 172.0 mg, 1 equiv., derived from R-(-)-2-amino-1-propanol via tempo oxidation and wittig olefination), (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (1.5 mmol, 348.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 48 hours. The mixture was diluted with ethyl acetate (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with ethyl acetate (50 ml) and the combined organic layers were thoroughly rinsed with 5% aq. K_2CO_3 and sat. aq. $NaHSO_3$ (Careful! Rapid Gas Evolution!) then dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield *tert*-butyl (*R*,3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ylcarbamate as a clear oil. Run 1 (223.3 mg, 0.82 mmol, 82%, >20:1 *E:Z*, >20:1 int.:term.); run 2 (216.5 mg, 0.79 mmol, 79%, >20:1

E:Z, >20:1 int.:term.). **Average Yield = 81%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 8 Hz, 2H), 7.21 (t, *J* = 7 Hz, 1H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 6.31 (dd, *J* = 15, 10.5 Hz, 1H), 5.77 (dd, *J* = 15, 5 Hz, 1H), 4.50 (br s, 1H), 4.34 (br s, 1H), 1.46 (s, 9H), 1.26 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.30, 137.42, 136.11, 132.46, 129.82, 128.80, 128.55, 127.68, 126.51, 79.57, 47.78, 28.62, 21.23. IR (neat, cm^{-1}) 3374.93, 3361.91, 3021.85, 2976.24, 2928.38, 2973.63, 1687.12. HRMS (ESI) *m/z* calculated for $C_{17}H_{23}NO_2Na$ $[M+Na]^+$: 296.1626, found 296.1627. $[\alpha]^{27}_D$ = +70.4 (c = 1.0, $CHCl_3$). Previously reported compound however no spectral data is given.[41]



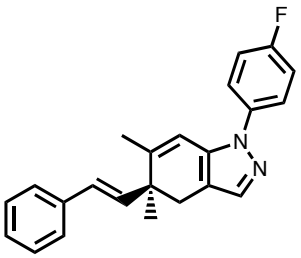
((R, 1*E*, 3*E*)-1-(2-bromophenyl)non-1,3-dien-5-yloxy)(*tert*-butyl)dimethylsilane: To a 2 mL borosilicate vial was added Catalyst **1** (0.025 mmol, 12.5 mg, 10 mol%), dimethylbenzoquinone (0.5 mmol, 68.0 mg, 2 equiv.), dioxane (0.25 mL, 1.0 M), acetic acid (1.0 mmol, 60.0 mg, 4 equiv.), (R)-*tert*-butyl(hept-1-en-3-yloxy)dimethylsilane (0.25 mmol, 57.0 mg, 1 equiv.), (E)-2-(2-bromostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.375 mmol, 115.5 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 48 hours. The mixture was diluted with methylene chloride (50 mL) and rinsed with water (50 ml). The aqueous layer was extracted with methylene chloride (50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 2 % ether:petroleum ether as eluent to yield ((R, 1*E*, 3*E*)-1-(2-bromophenyl)non-1,3-dien-5-yloxy)(*tert*-butyl)dimethylsilane as clear oil. Run 1 (122.1

mg, 0.30 mmol, 60%, >20:1 *E:Z*, >20:1 int.:term.); run 2 (120.0 mg, 0.29 mmol, 59%, >20:1 *E:Z*, >20:1 int.:term.). **Average yield = 60%** ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.55 (m, 2H), 7.26 (t, *J* = 5.6 Hz, 1H), 7.06 (dt, *J* = 7.6, 1.6 Hz, 1H), 6.86 (d, *J* = 15.6 Hz, 1H), 6.72 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.35 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.83 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.19 (q, *J* = 6.0 Hz, 1H), 1.55 – 1.47 (m, 2H), 1.35 – 1.25 (m, 4H), 0.91 (s, 9H), 0.90 – 0.86 (m, 3H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.65, 137.22, 133.28, 131.60, 130.13, 129.37, 128.70, 127.60, 126.59, 123.96, 73.42, 38.27, 27.62, 26.13, 22.90, 18.50, 14.28, -4.05, -4.55. IR (neat, cm^{-1}): 3055.22, 3030.17, 2954.31, 2929.11, 2857.55. HRMS (EI) *m/z* calculated for $C_{21}H_{33}BrOSi$ $[M+H]^+$: 408.14841, found 408.14855. $[\alpha]^{27}_D$ = +6.9° (c = 0.42, $CHCl_3$). Previously reported compound however no spectral data was given.[42]



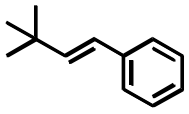
(*E*)-*tert*-butyl 5-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate: To an 8 mL borosilicate vial was added Catalyst 1 (0.04 mmol, 20.9 mg, 10 mol%), benzoquinone (0.82 mmol, 89.0 mg, 2 equiv.), dioxane (1.2 mL, 0.33 M), acetic acid (1.65 mmol, 96.1 mg, 4 equiv.), boric acid (0.82 mmol, 51.0 mg, 2 equiv.), 4-penten-1-ol (0.41 mmol, 35.0 mg, 1 equiv.), 1-(*tert*-butoxycarbonyl)-1*H*-indol-5-ylpotassium trifluoroborates (0.62 mmol, 200.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at room temperature for 4 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and rinsed with H_2O (50 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 30% ethyl

acetate/hexanes then further purified via silica chromatography (350 mL SiO_2) with 5% MeOH/CH_2Cl_2 as eluent to yield (*E*)-*tert*-butyl 5-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate as an oil. Run 1 (102.3 mg, 0.34 mmol, 82%, >20:1 *E:Z*, 16:1 int.:term., >20:1 int.:allyl.); run 2 (104.0 mg, 0.35 mmol, 84%, >20:1 *E:Z*, 16:1 int.:term., >20:1 int.:allyl.). **Average Yield = 83%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br d, *J* = 2.5 Hz, 1H), 7.57 (br d, *J* = 2.5 Hz, 1H), 7.51 (s, 1H), 7.35 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.54 (d, *J* = 3.5 Hz, 1H), 6.52 (d, *J* = 15 Hz, 1H), 6.24 (dt, *J* = 16, 6.5 Hz, 1H), 3.74 (t, *J* = 6 Hz, 2H), 2.35 (ap q, *J* = 7 Hz, 2H), 1.79 (ap p, *J* = 7 Hz, 2H), 1.68 (s, 9H), 1.40 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.91, 134.58, 132.64, 131.07, 130.82, 128.97, 126.48, 122.61, 118.55, 115.30, 107.57, 83.86, 62.71, 32.59, 29.60, 28.41. IR (neat, cm^{-1}) 3384.92, 3340.65, 3013.25, 2977.21, 2927.04, 2872.68, 1732.50. HRMS (ESI) *m/z* calculated for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1756, found 302.1753. Previously reported compound however no spectral data was given.[43]



(S,E)-1-(4-fluorophenyl)-5,6-dimethyl-5-styryl-4,5-dihydro-1*H*-indazole: To a 2 mL borosilicate vial was added Catalyst 1 (0.0099 mmol, 5.0 mg, 10 mol%), benzoquinone (0.18 mmol, 21.6 mg, 2 equiv.), dioxane (.3 mL, 0.33 M), acetic acid (0.4 mmol, 24.0 mg, 4 equiv.), (S)-1-(4-fluorophenyl)-5,6-dimethyl-5-vinyl-4,5-dihydro-1*H*-indazole (0.099 mmol, 26.5 mg, 1 equiv.), phenylboronic acid (0.2 mmol, 24.4 mg, 2 equiv.) and a stir bar sequentially under ambient conditions. The vial was capped and stirred at 45ºC for 3 days. The mixture was diluted with methylene chloride (50 mL) and rinsed with 3M NaOH (50 ml). The aqueous layer was extracted with methylene chloride

(50 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15 % ether:pentroleum ether as eluent to yield (S,E)-1-(4-fluorophenyl)-5,6-dimethyl-5-styryl-4,5-dihydro-1*H*-indazole as white solid. Run 1 (178.0 mg, 0.052 mmol, 52%, >20:1 *E:Z*); run 2 (187.0 mg, 0.054 mmol, 54%, >20:1 *E:Z*). **Average yield = 53%** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.44 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.20 (m, 3H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.33 (s, 1H), 6.24 (d, *J* = 16.0 Hz, 1H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.66 (d, J^1 C-F = 245.1 Hz), 145.49, 138.01, 137.82, 137.55, 136.13, 135.28, 128.75, 127.53, 127.47, 126.46, 125.50 (d, J^3 C-F = 8.3 Hz), 116.26 (d, J^2 C-F = 22.8 Hz), 114.66, 112.30, 42.32, 34.30, 23.48, 20.87. ^{19}F NMR (400 MHz, $CDCl_3$) δ -115.31. IR (neat, cm^{-1}): 3079.86, 3057.86, 3028.31, 2964.05, 2930.56, 2873.81, 2851.54, 2831.39, 1618.52, 1600.06. HRMS (ESI) *m/z* calculated for $C_{23}H_{22}FN_2$ $[M+H]^+$: 345.1767, found 345.1776. $[\alpha]^{25}_D$ = +95.0° (c = 0.38, $CHCl_3$, derived from 41.4% ee Hagemann's ester. See "Starting Material Synthesis for compound **21** on page S-15). Previously reported compound however no spectral data was given.[44]

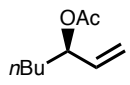


(*E*)-1-(3,3-dimethylbut-1-enyl)benzene: To a 40 mL borosilicate vial was added the following: catalyst **1** (0.1 mmol, 50.3 mg, 10 mol%), benzoquinone (2 mmol, 216.2 mg, 2 equiv.), 3,3-dimethyl-1-butene (1 mmol, 84.2 mg, 1 equiv.) in dioxane (3mL), acetic acid (4 mmol, 240 mg, 4 equiv.), tributylphenyltin (1.5 mmol, 550.7 mg, 1.5 equiv.), and a stir bar. The mixture was stirred at room temperature for 4 hours. The mixture was diluted with 40 mL of sat. aq. NH4Cl and extracted with

hexanes (2 x75 mL) and rinsed with 5% K2CO3 (1 x 75 mL). The organic layers were combined and dried over MgSO4. After concentration, the crude product was purified via silica gel chromatography (125 mL SiO2) with 100% hexanes as eluent to yield (*E*)-1-(3,3-dimethylbut-1-enyl)benzene as a clear oil. Run 1 (0.097 g, 0.60 mmol, 60%, >20:1 *E:Z*); run 2 (0.096 g, 0.60 mmol, 60%, 20:1 *E:Z*). **Average yield = 60%.** ^{1}H NMR (400 MHz, CDCl3) δ 7.39 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.34 (d, *J* = 16 Hz, 1H), 6.28 (d, *J* = 16 Hz, 1H), 1.16 (s, 9H). ^{13}C NMR (100 MHz, CDCl3) δ 142.0, 138.2, 128.7, 126.9, 126.2, 124.7, 33.6, 29.8. IR (neat, cm-1) 3025.38, 2960.48, 2903.23, 2866.92. HRMS (CI) *m/z* calculated for C12H17 [M+H]+: 161.1330, found 161.1330.

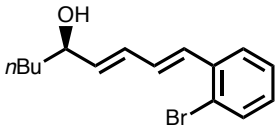
Internal Olefin: To an 8 mL borosilicate vial was added catalyst **1** (0.1 mmol, 50.2 mg, 10 mol%), benzoquinone (2.0 mmol, 216.0 mg, 2 equiv.), dioxane (3 mL, 0.33 M), acetic acid (4.0 mmol, 240.0 mg, 4 equiv.), trans-4-decene (1.0 mmol, 140.0 mg, 1 equiv.), phenylboronic acid (1.5 mmol, 183.0 mg, 1.5 equiv.) and a stir bar sequentially under ambient conditions. The vial as capped and stirred at room temperature for 4 hours. Nitrobenzene was used as an internal standard. NMR analysis of the crude mixture shows no conversion of the starting material.

%EE DETERMINATION

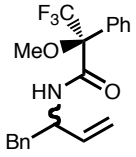


(*R*)-hept-1-en-3-yl acetate: Enantiopurity of the lipase resolved alcohol intermediate was determined by acetylation and chiral GC with a J&W Scientific Cyclodex-B, 30 meter, 0.25 mm diameter, 0.25 μm film column on a 5890

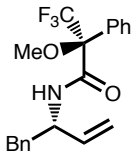
Hewlett Packard Series II GC, with a column flow rate 3.80 mL/min. Retention time of acetylated *R*-isomer was 8.187 min (*S*-isomer, 9.474 min) at an isothermal 65ºC. Enantiopurity was determined to be >99%.



((R, 1E, 3E)-1-(2-bromophenyl)non-1,3-dien-5-yloxy)(*tert*-butyl)dimethylsilane: Enantiopurity of the product was determined by TBAF deprotection to the corresponding alcohol followed by HPLC analysis with a Daicel Chemical Industries, LTD chiral OD-H, 0.46 cm x 25 cm column. A flow rate of 1.0 mL/min and 45 psi with 4% *i*-PrOH/hexanes eluent gave the *R*-isomer at 15.109 min and the *S*-isomer at 26.766 min. Enantiopurity was determined to be >99%.

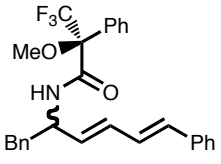


(*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-(1-phenylbut-3-en-2-yl)propanamide: All ratios reported from the crude spectrum. No chromatography performed. Diagnostic NMR peaks: ^{1}H (500 MHz, $CDCl_3$) δ 6.85 (br d, *J* = 9.0 Hz, 1H), 6.64 (br d, *J* = 8.5 Hz, 1H), 5.90 (m, 1H), 5.81 (m, 1H), 5.22 (d, *J* = 17.5 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz), 5.02 (d, *J* = 17.0 Hz, 1H). ^{19}F (376 MHz, $CDCl_3$) δ -69.16 (s, 3F), -69.39 (s, 3F).

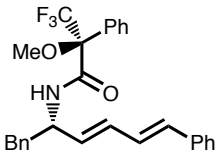


(*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*S*)-1-phenylbut-3-en-2-yl)propanamide: All ratios reported from the crude spectrum. No chromatography performed. Diagnostic NMR peaks: ^{1}H (500 MHz, $CDCl_3$)

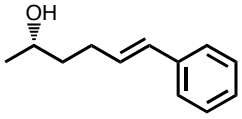
δ 6.64 (br d, *J* = 8.5 Hz, 1H), 5.81 (m, 1H), 5.09 (d, *J* = 10.5 Hz), 5.02 (d, *J* = 17.0 Hz, 1H). ^{19}F (470 MHz, $CDCl_3$) δ -69.16 (s, 3F). Enantiopurity was determined to be 98%.



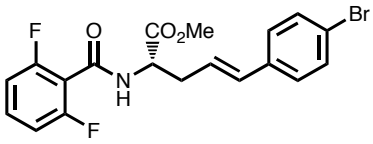
(*S*)-*N*-((3*E*,5*E*)-1,6-diphenylhexa-3,5-dien-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide: All ratios reported from the crude spectrum. No chromatography performed. Diagnostic NMR peaks: ^{1}H (400 MHz, $CDCl_3$) δ 6.51 (d, *J* = 15.6 Hz, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.34 (m, 1H), 6.10 (m, 1H), 5.81 (dd, *J* = 15.2, 6.0 Hz, 1H), 5.72 (dd, *J* = 15.2, 6.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.14 (s, 3F), -69.37 (s, 3F).



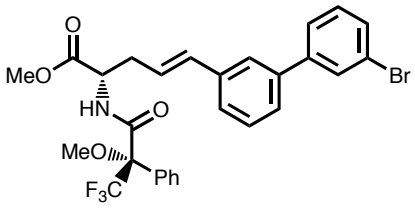
(*S*)-*N*-((*S*,3*E*,5*E*)-1,6-diphenylhexa-3,5-dien-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide: All ratios reported from the crude spectrum. No chromatography performed. Diagnostic NMR peaks: ^{1}H (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 16.0 Hz, 1H), 6.10 (m, 1H), 5.72 (dd, *J* = 15.2, 6.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.12 (s, 3F). Enantiopurity was determined to be 98%.



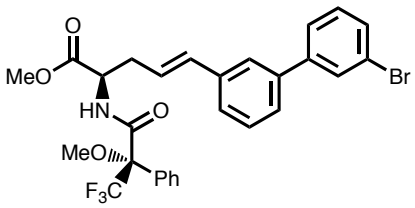
(*S*,*E*)-6-phenylhex-5-en-2-ol: Enantiopurity was determined by HPLC analysis with a Daicel Chemical Industries, LTD chiral OD-H, 0.46 cm x 25 cm column. A flow rate of 1.0 mL/min and 45 psi with 5% *i*-PrOH/hexanes eluent gave the *S*-isomer at 16.598 min and the *R*-isomer at 18.678 min. Enantiopurity was determined to be >99%.



(*S*,*E*)-methyl 5-(4-bromophenyl)-2-(2,6-difluorobenzamido)pent-4-enoate: Enantiopurity was determined via Heck-arylation beginning from opposite enantiomers, followed by HPLC analysis with a Daicel Chemical Industries, LTD chiral OD-H, 0.46 cm x 25 cm column. A flow rate of 1.0 mL/min and 45 psi with 5.0% *i*-PrOH/hexanes eluent gave the *R*-isomer at 19.67 min and the *S*-isomer at 18.19 min. Enantiopurity was determined to be >99%.

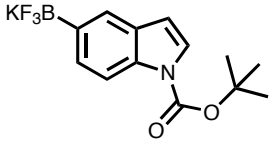


(*S*,*E*)-methyl 5-(phenyl-3-(bromo-3-phenyl))-2-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pent-4-enoate: All ratios reported from the crude spectrum. No chromatography preformed. Diagnostic NMR peaks: ^{1}H (500 MHz, $CDCl_3$) δ 6.57 (d, *J* = 15.0 Hz, 1H), 6.15 (dt, *J* = 15.5, 7.5 Hz, 1H), 4.82 (ap q, *J* = 6.5 Hz, 1H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -69.36 (s, 3F). Enantiopurity was determined to be >95%.



(*R*,*E*)-methyl 5-(phenyl-3-(bromo-3-phenyl))-2-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pent-4-enoate: All ratios reported from the crude spectrum. No chromatography preformed. Diagnostic NMR peaks: ^{1}H (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 15.5 Hz, 1H), 6.01 (dt, *J* = 15.5, 7.5 Hz, 1H), 4.89 (m, 1H), . ^{19}F NMR (470 MHz, $CDCl_3$) δ -69.15 (s, 3F). Enantiopurity was determined to be >95%.

STARTING MATERIALS SYNTHESIS REFERENCES:



1-(*tert*-butoxycarbonyl)-1*H*-indol-5-ylpotassium trifluoroborate: A 50 mL round bottomed flask (RBF) was charged with a stir bar, *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (0.805 g, 2.3 mmol), ether (4 mL), and methanol (7 mL). Aqueous 3M KF_2H (4.4 mL, 13.1 mmol) was added dropwise at room temperature. The mixture was stirred for 2 hours. The stir bar was removed and the solvents removed via rotary evaporation. Boiling acetone was added, and the hot solution was filtered. The filtrate was concentrated and dissolved in <20 mL of warm acetone. Petroleum ether (200 mL) was added to the mixture and the solution was undisturbed for 2 hours. The white precipitate was filtered off and rinsed with cold petroleum ether (50 mL) to award the title compound as a white solid (0.650 g, 2.0 mmol, 86%). ^{1}H NMR (500 MHz, d_6-acetone) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 4 Hz, 1H), 6.52 (d, *J* = 4 Hz, 1H), 1.68 (s, 9H). ^{19}F NMR (470 MHz, d_6-acetone) δ -142.24. ^{13}C NMR (125 MHz, $(CH_3)_2CO$) δ 150.65, 135.13, 130.53, 129.30, 125.01, 124.81, 113.92, 108.59, 83.50, 28.30, (C *ipso* to B not observed). IR (neat, cm^{-1}): 3033.33, 2974.38, 2930.04, 1730.97, 992.97. HRMS (CI) *m/z* calculated for $C_{13}H_{14}NO_2BF_3K$ $[M+H]^+$: 284.1070, found 284.1071.[30]

*Enantiomeric excess (%ee) was determined based off of optical rotation according to the equation %ee = (100 $[\alpha]_{obs}$)/$[\alpha]_{lit.\ ref\ 31}$, %ee = (100 $[53.4]^{23}_D$)/$[129]^{23}_D$ = 41.4 % ee.

2.5 REFERENCES

[1] (a) Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions:* de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Crisp, G. T.; *Chem. Soc. Rev.* **1998**, *27*, 427. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (e) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.

[2] (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (c) Jeffery, T. *Tetrahedron Lett.* **2000**, *41*, 8445.

[3] (a) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85. (b) Lindh, J.; Enquist, P.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957. (c) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729.

[4] Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.

[5] (a) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1993**, *34*, 1643. (b) Kang, S. –K.; Lee, H. –W.; Jang, S. –B.; Kim, T. –H.; Pyun, S. –J. *J. Org. Chem.* **1996**, *61*, 2604. (c) Olofsson, K.; Sahlin, H.; Larhead, M; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544. (d) Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890.

[6] (a) Wagner, R.; Tilley, J. *J. Org. Chem.* **1990**, *55*, 6289. (b) Kabawata, N. W.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1992**, *45*, 513. (c) Shimamoto,

K.; Shigeri, Y.; Yasuda-Kamatani, Y.; Lebrun, B.; Yumoto, N.; Nakajima, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407.

[7] (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) North, M. *J. Peptide Sci.* **2000**, *6*, 301.

[8] (a) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans, 1* **1994**, 1411. (b) Cohen, J. H.; Abdel-Magid, A. F.; Almond, H. R.; Maryanoff, C. A. *Tetrahedron Lett.* **2002**, *43*, 1977. (c) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635.

[9] Angeluad, R.; Zhong, Y. –L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949.

[10] (a) Qu, D.; Ludwig, D. S.; Grammeltoft, S.; Piper, M.; Pelleymounter, M. A.; Cullen, M. J.; Mathes, W. F.; Przypek, J.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243. (b) Rossi, M.; Choi, S. J.; O'Shea, D.; Miyoshi, T.; Ghatei, M. A.; Bloom, S. R. *Endocrinology* **1997**, *138*, 351.

[11] Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; Deleon, J.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *8*, 825.

[12] Kanuma, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Nagase, Y.; Iida, I.; Yamaguchi, J.; Semple, G.; Tran, T.; Sekiguchi, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3307.

[13] (a) Tomasselli, A. G.; Heinrikson, R. L.; *Biochim. Biophys. Acta* **2000**, *1477*, 189. (b) Richman, D. D. *Nature* **2001**, *410*, 995. (c) Brik, A.; Wong, C. –H. *Org. Biomol. Chem.* **2003**, *1*, 5.

[14] Tossi, A.; Benedetti, F.; Norbedo, S.; Skrbec, D.; Berti, F.; Romeo, D. *Bioorg. Med. Chem.* **2003**, *11*, 4719.

[15] Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505.

[16] Wu, Y.-Q.; Wilkinson, D. E.; Limburg, D.; Li, J.-H.; Sauer, H.; Ross, D.; Liang, S.; Spicer, D.; Valentine, H.; Fuller, M.; Guo, H.; Howorth, P.; Soni, R.; Chen, Y.; Steiner, J. P.; Hamilton, G. S. *J. Med. Chem.* **2002**, *45*, 3558.

[17] Lambert, J. D.; Rice, J. E.; Hong, J.; Hou, Z.; Yang, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.

[18] (a) Larock, R.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2005**, *20*, 3589.

[19] (a) Whitehouse, D.; Hu, S.; Van Zandt, M. C.; Parker, G. U.S. Patent 055725, 2006. (b) Hirano, N.; Inoue, H.; Nagahara, T.; Ohyama, T.; Kaino, M.; Hayashi, K.; Hara, S.; Suzuki, R. U.S. Patent 068213, 2006.

[20] Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2005**, *48*, 5329.

[21] Duan, J.; Lu, Z.; Weinstein, D.; Jiang, B. U.S. Patent 138373, 2006.

[22] (a) Kelly, M.; Kincaid, J.; Duncton, M.; Sahasrabudhe, K.; Janagani, S.; Upasani, R. B.; Wu, G.; Fang, Y.; Wei, Z.; Kaub, C. U.S. Patent WO 093832, 2006. (b) Upasani, R. B.; Kelly, M. G.; Janagani, S. Patent WO 2005/046683. (c) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130.

[23] For a review of BF_3K reagents see: Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

[24] Ackermann, J.; Aebi, J.; Dehmlow, H.; Morand, O.; Panday, N.; Weller, T. U.S. Patent WO 044149, 2002.

[25] Yuen, A.; Hutton, C. *Tetrahedron Lett.* **2005**, *46*, 7899.

[26] Gaeta, F. C. A.; Lehman de Gaeta, L. S.; Kogan, T. P.; Or, Y.; Foster, C.; Czarniecki, M. *J. Med. Chem.* **1990**, *33*, 964.

[27] Petasis, N. A. U.S. Patent WO 0203184, 2005.

[28] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[29] Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752.

[30] Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **2005**, *48*, 5329.

[31] Lambert, J. D.; Rice, J. E.; Hong, J.; Hou, Z.; Yang, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.

[32] Wu, Y. Q.; Wilkinson, D. E.; Limburg, D.; Li, J. H.; Sauer, H.; Ross, D.; Liang, S.; Spicer, D.; Valentine, H.; Fuller, M.; Guo, H.; Howorth, P.; Soni, R.; Chen, Y.; Steiner, J. P.; Hamilton, G. S. *J. Med. Chem.* **2002**, *45*, 3558.

[33] Whitehouse, D.; Hu, S.; Van Zandt, M. C.; Parker, G. US Patent: 055725, 2006.

[34] Hirano, N.; Inoue, H.; Nagahara, T.; Ohyama, T.; Kaino, M.; Hayashi, K.; Hara, S.; Suzuki, R. US Patent: 068213, 2006.

[35] Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446.

[36] Benedetti, F.; Miertus, S.; Norbedo, S.; Tossi, A.; Zlatoidzky, P. *J. Org. Chem.* **1997**, *62*, 9348.

[37] Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505.

[38] Angelaud, R.; Zhong, Y. L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949.

[39] Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Nagase, Y.; Iida, I.; Yamaguchi, J.; Semple, G.; Tran, T.; Sekiguchi, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3307.

[40] Gaeta, F. C. A.; Lehman de Gaeta, L. S.; Kogan, T. P.; Or, Y. S.; Foster, C.; Czarniecki, M. *J. Med. Chem.* **1990**, *33*, 964.

[41] Dellaria, J. F.; Sallin, K. J. *Tetrahedron Lett.* **1990**, *31*, 2661.

[42] Petasis, N. A. US Patent: 0203184, 2005.

[43] Ackermann, J.; Aebi, J.; Dehmlow, H.; Morand, O.; Panday, N.; Weller, T. US Patent: 02/44149, 2002.

[44] Duan, J.; Lu, Z.; Weinstein, D. S.; Jiang, B. US Patent 138373, 2006.

CHAPTER 3

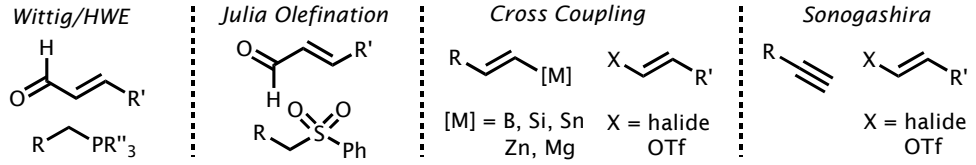
AN INTERMOLECULAR OXIDATIVE HECK VINYLATION WITH LIMITING α-OLEFIN

3.1 INTRODUCTION

Polyenes are prevalent moieties in natural products and pharmaceuticals. The synthesis of polyenes have several important synthetic requirements:[1] (1) Mild conditions are necessary due to problematic isomerizations in the presence of light, oxygen and many synthetic reagents.[2] (2) Broad functional group tolerance is needed because polyenes are generally installed late in synthetic routes amid diverse functionality due to their sensitive nature. (3) Highly stereoselective methods are a prerequisite for polyene synthetic strategies because olefin isomers are often inseparable.

Current polyene synthetic strategies require either (1) carbonyl olefinations or (2) transition metal based cross-coupling reactions (figure 24).[1,3] The Wittig, Horner-Wadsworth-Emmons (HWE), and Julia olefination reactions are commonplace when constructing polyene segments; however, *E:Z* selectivities are frequently problematic. The Stille, Suzuki, Negishi, and Sonagashira cross-coupling reactions are mild, functional

Figure 24. Polyene synthetic strategies for complex molecule synthesis.

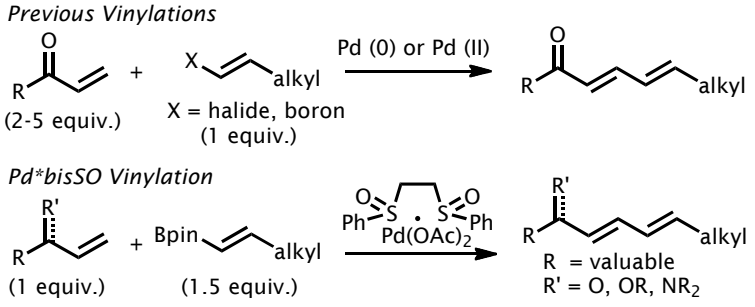


group tolerant and give excellent selectivities for polyene synthesis. Yet these cross-couplings, like olefination strategies, require prior activation of both coupling partners (and a subsequent reduction for the Sonogashira reaction specifically).

The intermolecular Heck reaction is unique among palladium-based cross-coupling reactions due to the direct formation of C-C bonds from the vinylic C-H bonds of α-olefins, which necessitates prior activation of only one coupling partner.[4] Mild, selective C-H bond transformations in the presence of valuable, diverse functionality are known to simplify and streamline synthetic sequences when compared to methods dependant on pre-functionalization.[5] In the Heck vinylation, the activated coupling partner may be either a vinyl halide or a vinyl transmetalating reagent. The direct synthesis of stereodefined vinyl halides is often problematic without first synthesizing a carbon-metalated intermediate. Significantly, *oxidative* Heck vinylations[6] forego the synthesis of stereodefined vinyl halide coupling partners which are often formed through intermediate vinyl boron species.[7] These vinyl boron transmetalating reagents may be coupled directly and are easily synthesized with high stereoselectivities through a variety of methods.[8]

Despite the tremendous advantages of polyene synthesis via the intermolecular Heck vinylation, application in complex molecule synthesis has not been realized due to (1) a large excess of the α-olefin coupling partner being needed and (2) limited α-olefin substrate scope (figure 25). Generally, resonance bias of the terminal olefin is necessary

Figure 25. Comparison of Heck vinylations.



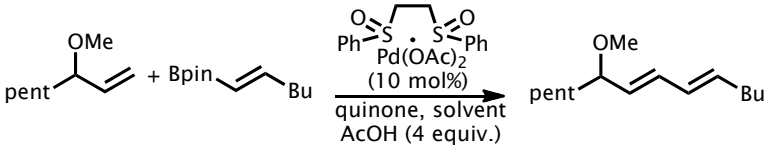
to control the regioselectivity of insertion, to control direction of β-hydride elimination, and to increase reactivity of the α-olefin. These requirements limit the olefin scope to primarily α,β-unsaturated-carbonyls and styrenes.[9] We reported the development of a palladium II-based intermolecular *oxidative* Heck vinylation which proceeds in good yields and selectivities with a wide range of non-resonance stabilized terminal olefins as the limiting reagent.

3.2 RESULTS AND DISCUSSION

3.2.1 Development of an Oxidative Heck Strategy for Polyene Synthesis with Limiting Terminal Olefin

The oxidative Heck vinylation reported herein is promoted by commercial palladium (II)/bis-sulfoxide catalyst **1** under oxidative, mild conditions which generate polyene products in preparatively useful yields with excellent regio- and *E/Z* stereoselectivities.[10] Previously, we reported a palladium (II)/bis-sulfoxide catalyzed arylation of non-resonance activated α-olefins with arylboronic acids.[11] Attempts to

Table 7. Optimization of an oxidative Heck-vinylation.



entry	quinone (equiv.)	solvent (molarity)	variable	isolated yield[a,b]
1	BQ (2.0)	THF (0.33 M)	boronic acid	0%
2	BQ (2.0)	THF (0.33 M)	---	16%
3	Me_2BQ (2.0)	THF (0.33 M)	---	43%
4	Me_2BQ (2.0)	THF (2.0 M)	---	49%
5	Me_2BQ (1.1)	DMF (2.0 M)	O_2 atmosphere	55%
6	Me_2BQ (1.1)	DMF (2.0 M)	20 mol% H_2O	41%
7	Me_2BQ (1.1)	DMF (2.0 M)	no ligand	9%

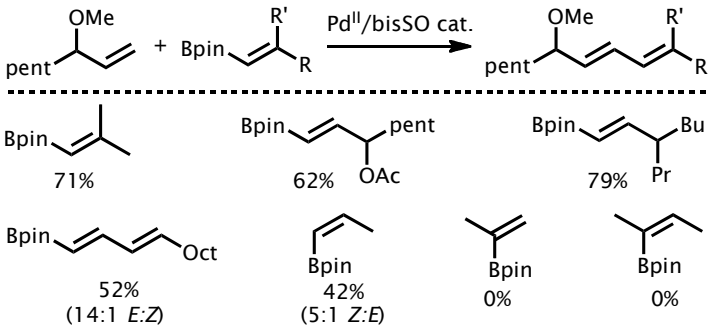
[a] Average of 2 runs. [b] >20:1 *E:Z* and >20:1 internal:terminal selectivities determined by crude NMR for all entries unless otherwise noted.

utilize vinyl boronic acids resulted in complete consumption of the vinyl boron and no desired product formation (table 7, entry 1). However, the more stable vinyl pinacol

boronic ester gave the desired product in 15% yield (table 7, entry 2). We hypothesized side reactions with benzoquinone could be problematic since insertion is favorable with sterically accessible activated olefins, and we observed depletion of the boronic ester. Accordingly, changing the benzoquinone oxidant to the more hindered 2,6-dimethylbenzoquinone gave a dramatic increase in yield to 43% (table 7, entry 3). Standard optimizations of molarity, oxidant equivalents and solvent further increased the yield to 55% (table 7, entries 4 and 5). Water was found to be detrimental, and oxygen atmosphere had no adverse effects when compared to inert atmosphere (table 7, entries 5 and 6). Bis-sulfoxide ligand also proved crucial for this reaction, whereas $Pd(OAc)_2$ gave only 9% yield (table 7, entry 7).

Examination of the vinyl boron component indicated a wide range of vinyl boron reagents couple under these optimized conditions (figure 26). In addition to *trans*

Figure 26. Vinylboronic ester coupling partner scope.



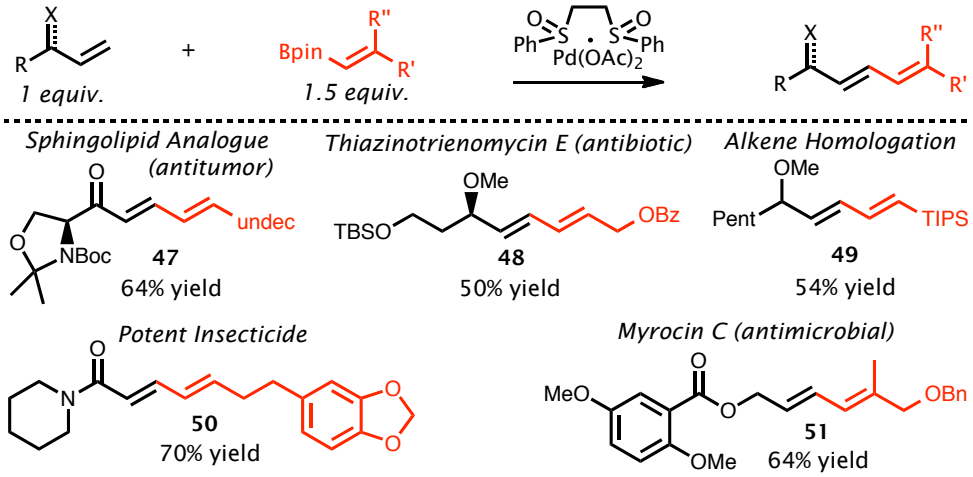
disubstituted boron reagents, trisubstituted boronic esters couple smoothly. Vinyl boron reagents with substitution in the allylic position are also excellent coupling partners. Interestingly, increasing steric bulk closer to the reactive vinyl boron site increased product yield, presumably by slowing homo-coupling pathways. Higher order polyene products are synthetically accessible in preparative yields by coupling polyunsaturated vinylic boronic esters. *Importantly, E:Z ratios were >10:1 and internal:terminal olefin*

ratios >14:1 in all examined cases of trans monosubstituted, disubstituted and polyunsaturated vinylic boron reagents. Under these conditions *cis* monosubstituted vinylic boronic esters gave low yield and lower stereoselectivity (from >20:1 *Z:E* [boron reagent] to 5:1 *Z:E* [product]). Furthermore, all attempts to couple 1-substituted vinyl boron starting materials gave no conversion of the boron coupling partner or terminal olefin, even at elevated temperatures. Presumably, catalyst **1** is highly sensitive to steric bulk alpha to the boron atom since the only cases where transmetalation fails are on boron reagents with alpha substitution present.

3.2.2 Accessing Medicinally Interesting Motifs with a Novel Oxidative Heck Vinylation

Complex polyene products are not commonly accessed through Heck reactions due to the necessity of a resonance activated α-olefin in excess (typically 3-5 equiv.). In contrast, the **1** catalyzed oxidative Heck reaction operates with limiting α-olefin; the use of coupling stoichiometries allows the streamlining potential of the Heck reaction to be utilized in the synthesis of complex, medicinally relevant molecules (figures 27-30). Furthermore, both resonance activated and non-resonance activated α-olefins with allylic substitution proved effective coupling partners (figure 27). Molecules important for cell growth and differentiation (**47**) as well as a segment of a complex antibiotic (**48**) with epimerizable α-keto- and allylic ether stereocenters retained stereochemical information during the oxidative Heck coupling.[12] Compounds **50** and **51**, which utilize valuable boron coupling partners, are practically synthesized because only a slight excess of vinyl boron starting material is needed.[13] Both of these molecules are being pursued for their biological activities toward insects and microbes respectively. An ethylene TIPS boronic

Figure 27. Synthetic intermediates accessable through oxidative Heck vinylation.



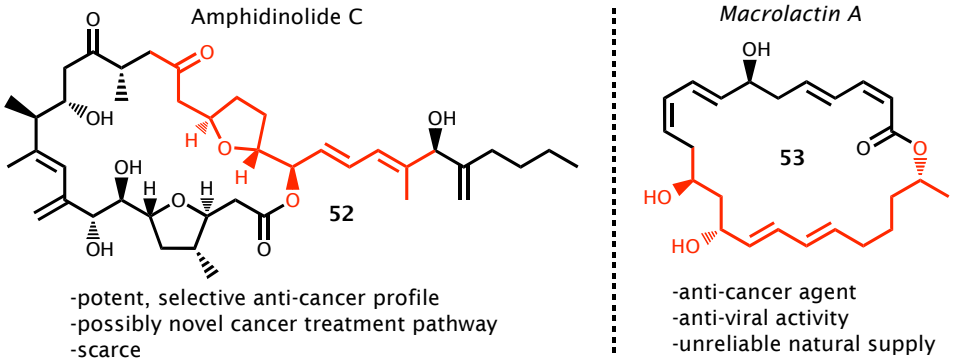
ester coupled in synthetically useful yields to give the ethylene homologated TIPS product **49**, which is amenable to further reactions.

3.2.3 Synthetic Comparison of the Oxidative Heck to Olefination and Transition Metal Cross-Coupling Reactions

We sought to compare **1** catalyzed Heck based synthetic strategies to each type of prominent polyene formation strategies. Intermediates to two complex natural products, amphidinolide C (**52**) and macrolactin A (**53**), were chosen as targets (figure 28). The amphidinolide C segment was synthesized through an olefination method, while the macrolactin A segment was formed through a transition metal mediated cross-coupling reaction.

Amphidinolide C is a scarce, potent anticancer agent which has drawn attention synthetically because of both the importance of analogues to understand its bioactivity, and its interesting macrocyclic structure. A previous synthesis of the highlighted segment of amphidinolide C was undertaken to prove the absolute stereochemistry of each stereocenter in the segment. The key disconnect for the highlighted fragment of **52**

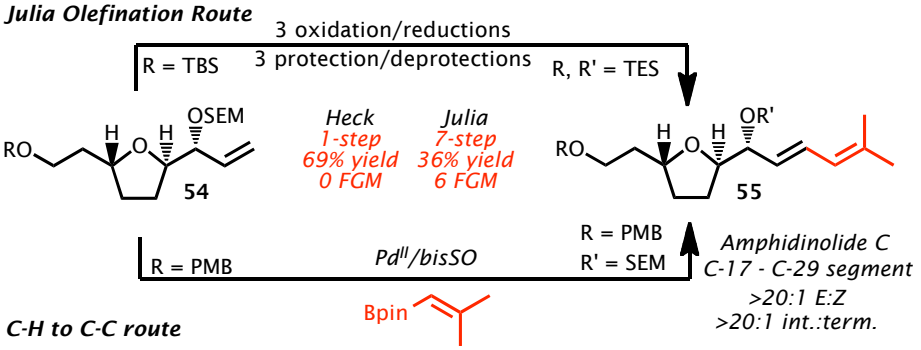
Figure 28. Complex natural products with highlighted diene segments.



was a Julia olefination, which requires installation of sulfur functionality, condensation with an aldehyde, and elimination of the sulfur motif. As previously mentioned, the stereoselectivity of the alkene formed during this olefination is often difficult to predict. Beginning from olefin intermediate **54**, protecting group changes were necessary to achieve good *E:Z* selectivities for the desired diene segment (figure 29).

When compared to a carbonyl olefination route, the power of this oxidative Heck reaction to streamline synthesis was observed by synthesizing the C17-C29 segment of Amphidinolide C, **52** (figure 29).[14] Beginning from the same α-olefin intermediate **54**

Figure 29. Amphidinolide C segment synthesis: Julia olefination vs oxidative Heck route.

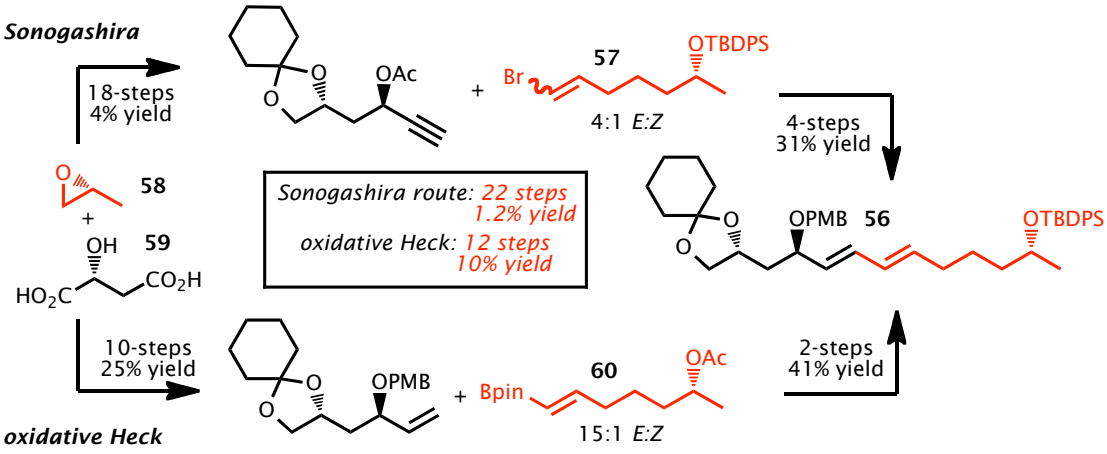


used in the olefination route, the diene moiety **55** was synthesized in a single step in 69% yield, which compares favorably to the 36% yield over 7-steps achieved via a Julia olefination route. As mentioned, Julia olefination selectivities are often dependant on

protecting group choice, as is observed in this case. Strikingly, the oxidative Heck vinylation gave good selectivities (>20:1 *E:Z*) with no protecting group manipulations.

Macrolactin A is a biologically active molecule with possible anti-cancer and anti-viral applications; however, complete biological studies have not been realized due to an unreliable natural supply. The synthesis of the highlighted segment of macrolactin A in figure 28 was previously undertaken with the key bond forming step being a Sonagashira coupling/alkyne reduction sequence to form intermediate **56** (figure 30). When synthesizing the stereodefined vinyl bromide **57**, only modest stereoselectivity was achieved (4:1 *E:Z*). Furthermore, the vinyl halide **57** was synthesized through a carbon-metalated intermediate which under oxidative transition metal mediated conditions could possibly be coupled directly. Furthermore, the reduction of the ene-yne functionality to a diene requires conditions which are not compatible with several protecting groups, as evidenced by the necessary switch from an allylic acetate to the desired allylic PMB ether later in the sequence.

Figure 30. Macrolactin A intermediate synthesis: Sonogashira vs oxidative Heck route.

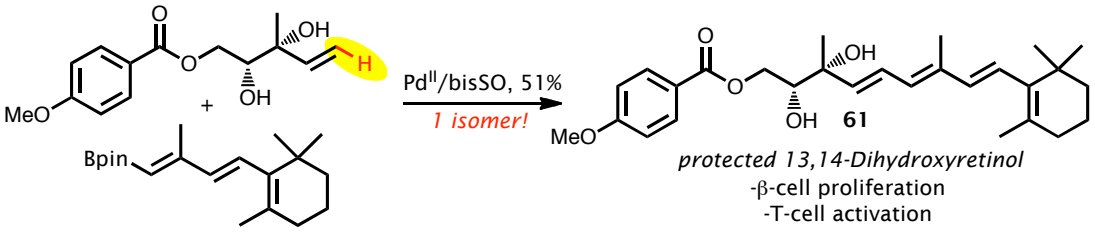


We compared the recently developed oxidative Heck vinylation to this common transition metal based cross-coupling strategy for polyene formation. Beginning again

from identical starting materials **58** and **59**, the C12-C24 segment of macrolactin A, **56**, was synthesized in 10 fewer steps and 8 times greater yield (figure 30).[15] Significantly, the stereodefined vinyl boron intermediate **60** was accessed in better yields, fewer steps, and higher regioselectivities than the analogous vinyl bromide **57** for the Sonagashira route. It is often beneficial to expose conjugated polyunsaturated functionality to minimal reagents since isomerizations are often problematic. Importantly, the delicate polyunsaturated functionality is installed later in the Heck route for the synthesis of **56** than in the Sonagashira route (2 steps vs. 4 steps to **56** after the key coupling).

Members of the retinoid family such as **61** have been synthesized through a large number of palladium mediated cross coupling reactions including Suzuki, Stille, Hiyama, Negishi, and Kumada couplings.[16] However, the Heck reaction has yet to be used to access a member of this family since polyene functionality is not conventionally installed using this method. Also, accessing a member of the retinoid family requires a coupling reaction with near equimolar stoichiometry of the coupling partners, since both fragments are complex. As shown in figure 25, previous intermolecular Heck reactions required an excess of the terminal olefin coupling partner. The excess complex fragment precluded the use of a practical Heck reaction to access the retinoid family. With our new oxidative manifold, a terminal olefin may be used as the limiting reagent; additionally our mild conditions allow for the synthesis of large, delicate polyenes with good selectivities. The tetraene retinoid **61** was formed in synthetically useful yield with catalyst **1**, giving to the best of our knowledge the longest contiguous polyene synthesized via Heck reaction to date (figure 31).

Figure 31. Longest polyene via Heck reaction.



Notably, an unprotected diol was successfully coupled with a trienyl boronic ester furnishing a single isomer of **61**. The observed selectivities testify to the mild, selective nature of this manifold.

3.3 CONCLUSIONS

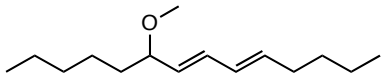
The oxidative Heck reaction reported in this chapter offers an alternative synthetic strategy to polyene formation which requires activation of only one vinylic carbon. This method is amendable to complex molecule synthesis as demonstrated by 13 examples that only require coupling quantities of each partner. Limiting equivalents of terminal olefin compares favorably to the excessive amounts of α-olefin coupling partner typically required of the Heck reaction. Importantly, this mild manifold allows for installation of delicate polyene functionality late in synthetic sequences, with good stereoselectivity.

3.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents for the Heck arylation reaction were used as received: 1,4-benzoquinone and 2,6-dimethylbenzoquinone (Sigma-Aldrich); 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate "Catalyst **1**" (Strem, TCI, Sigma-Aldrich). Catalyst **1** was stored in a glove box under an argon

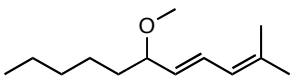
atmosphere and weighed out in air prior to use. Solvents dioxane, tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N,N-dimethylformamide (DMF) (Sure Seal) was obtained from Sigma-Aldrich and used as received. All Heck vinylation reactions were run under N_2 with minimal exposure to moisture. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate staining. Flash column chromatography was performed as described by Still using EM reagent silica gel 60 (230-240 mesh).[17] ^1H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). ^{19}F NMR spectra were recorded on a Varian Unity-400 (376 MHz) or Varian-500 (470 MHz) spectrometer and are reported in ppm using a 1% $C_6F_6/CDCl_3$ standard referenced to -164.3 ppm. Regioselectivity of the Heck addition was determined by NMR analysis of the crude mixture. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were obtained using a JAS.CO DIP-370 digital polarimeter and a 3.5 x 100 mm cell.

General Procedure: To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.1 mmol, 10 mol%) and 2,6-dimethylbenzoquinone (1.1 mmol, 1.1 equiv.) in one portion. The following liquids were added via syringe through the septum sequentially: DMF (0.5 mL, 2.0 M), acetic acid (4.0 mmol, 4 equiv.), terminal alkene coupling partner (1.0 mmol, 1.0 equiv.) and vinylic boronic ester coupling partner (1.5 mmol, 1.5 equiv.). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography. The crude selectivities were determined by ^{1}H NMR.



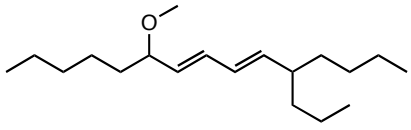
(5*E*,7*E*)-9-methoxytetradeca-5,7-diene: To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv.). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv.), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv.) and (*E*)-2-(hex-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.75 mmol, 158.0 mg, 1.5 equiv.). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing

the vial with stirring at 40°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (5*E*,7*E*)-9-methoxytetradeca-5,7-diene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (63.8 mg, 0.29 mmol, 57%); run 2 (61.6 mg, 0.28 mmol, 55%); run 3 (60.5 mg, 0.27 mmol, 54%). **Average Yield = 55%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14–5.99 (m, 2H), 5.67 (dt, *J* = 14.8, 6.8 Hz, 1H), 5.35 (dd, *J* = 14.8, 8.4 Hz, 1H), 3.48 (apt. q, *J* = 6.4, 1H), 3.22 (s, 3H), 2.06 (apt. q, *J* = 6.8 Hz, 2H), 1.62-1.50 (m, 2H), 1.48-1.18 (m, 10H), 0.92-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.1, 131.7, 129.7, 82.6, 56.3, 35.9, 32.5, 32.1, 31.6, 25.3, 22.8, 22.5, 14.3, 14.2. IR (neat, cm^{-1}) 3016, 2956, 2929, 2872, 2860, 2819. HRMS (EI) *m/z* calculated for $C_{15}H_{28}O$ $[M]^+$: 224.2140, found 224.2140.



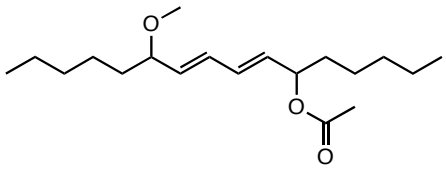
(*E*)-6-methoxy-2-methylundeca-2,4-diene: To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv.). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv.), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv.) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (0.75 mmol, 136.5 mg, 1.5 equiv.). A stir bar

was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-6-methoxy-2-methylundeca-2,4-diene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (68.6 mg, 0.35 mmol, 70%); run 2 (69.6 mg, 0.36 mmol, 71%). **Average Yield = 71%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.82 (d, *J* = 11.2 Hz, 1H), 5.34 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.52 (apt. q, *J* = 8.0 Hz, 1H), 3.23 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.62-1.50 (m, 1H), 1.48-1.37 (m, 1H), 1.37-1.18 (m, 6H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 131.4, 129.3, 124.6, 82.9, 56.2, 36.0, 32.1, 26.2, 25.3, 22.8, 18.5, 14.3. IR (neat, cm^{-1}) 3018, 2958, 2929, 2858, 2817. HRMS (EI) *m/z* calculated for $C_{13}H_{24}O$ $[M]^+$: 196.1827, found 196.1825.



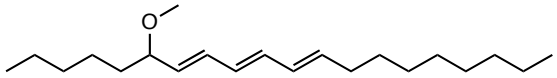
(6*E*,8*E*)-10-methoxy-5-propylpentadeca-6,8-diene: To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv.). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid

(2.0 mmol, 132.0 mg, 4.0 equiv.), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv.) and (*E*)-4,4,5,5-tetramethyl-2-(3-propylhept-1-enyl)-1,3,2-dioxaborolane (0.75 mmol, 200.0 mg, 1.5 equiv.). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (6*E*,8*E*)-10-methoxy-5-propylpentadeca-6,8-diene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. 20:1 and *E:Z* >20:1. Run 1 (110.6 mg, 0.40 mmol, 79%); run 2 (110.6 mg, 0.40 mmol, 79%). **Average Yield = 79%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.99 (dd, *J* = 15.0, 10.0 Hz, 1H), 5.44 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.38 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.52 (apt. q, *J* = 7.5 Hz, 1H), 3.27 (s, 3H), 2.02-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.52-1.42 (m, 1H), 1.42-1.16 (m, 16H), 0.96-0.82 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 133.2, 131.5, 129.3, 82.6, 56.3, 42.8, 37.8, 35.9, 35.3, 32.1, 29.7, 25.3, 23.1, 22.8, 20.6, 14.4, 14.3 (2C). IR (neat, cm^{-1}) 3016, 2954, 2929, 2872, 2860, 2818. HRMS (EI) *m/z* calculated for $C_{19}H_{36}O$ $[M]^+$: 280.2766, found 280.2775.



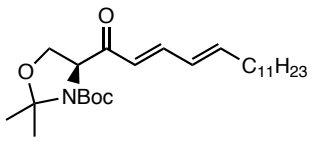
(7*E*,9*E*)-11-methoxyhexadeca-7,9-dien-6-yl acetate: To a flame dried 2 mL borosilicate vial with

a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv.). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv.), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv.) and (*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-1-en-3-yl acetate (0.75 mmol, 222.0 mg, 1.5 equiv.). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 7% ethyl acetate/hexanes as eluent to yield (7*E*,9*E*)-11-methoxyhexadeca-7,9-dien-6-yl acetate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (93.0 mg, 0.30 mmol, 60%); run 2 (97.7 mg, 0.32 mmol, 63%). **Average Yield = 62%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26–6.04 (m, 2H), 5.57 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.51 (dd, *J* = 14.8, 7.6 Hz, 1H), 5.23 (apt. q, *J* = 6.8 Hz, 1H), 3.51 (apt. q, *J* = 7.6 Hz, 1H), 3.23 (s, 3H), 2.03 (s, 3H), 1.68-1.48 (m, 3H), 1.48-1.36 (m, 1H), 1.36-1.16 (m, 12H), 0.90-0.80 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 135.6 (d), 131.9 (d), 131.6, 131.5, 82.3, 74.6 (d), 56.5, 35.8, 34.6, 32.0, 31.8, 25.2 (d), 25.0, 22.8, 22.7, 21.6, 16.5, 14.3 (d). IR (neat, cm^{-1}) 3023, 2956, 2931, 2860, 2819, 1739. HRMS (EI) *m/z* calculated for $C_{19}H_{34}O_3$ $[M]^+$: 310.2508, found 310.2508.



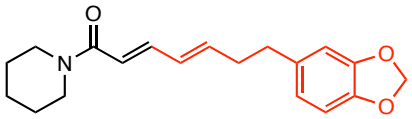
(7*E*,9*E*,11*E*)-6-methoxyicosa-7,9,11-triene: To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv.). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv.), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv.) and 2-((1*E*,3*E*)-dodeca-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.75 mmol, 219.0 mg, 1.5 equiv.). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (7*E*,9*E*,11*E*)-6-methoxyicosa-7,9,11-triene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* 14:1. Run 1 (78.0 mg, 0.26 mmol, 51%); run 2 (81.1 mg, 0.27 mmol, 53%). **Average Yield = 52%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26–5.86 (m, 4H), 5.73 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.47 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.55 (apt. q, *J* = 8.4 Hz, 1H), 3.26 (s, 3H), 2.10 (apt. q, *J* = 6.8 Hz, 2H), 1.68-1.54 (m, 1H), 1.52-1.16 (m, 19H), 0.96-0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 133.5 (2C), 133.0, 130.3, 129.8, 82.6, 56.3, 35.9, 33.0, 32.1 (2C), 29.7, 29.5, 29.4, 25.3, 22.9, 22.8, 14.3 (2C). IR (neat, cm^{-1}) 3016,

2956, 2927, 2854. HRMS (EI) *m/z* calculated for $C_{21}H_{38}O$ $[M]^+$: 306.2923, found 306.2931.



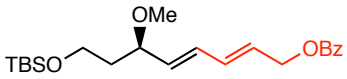
(*S*)-*tert*-butyl 4-((2*E*,4*E*)-hexadeca-2,4-dienoyl)-2,2-dimethyloxazolidine-3-carboxylate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*S*)-*tert*-butyl 4-acryloyl-2,2-dimethyloxazolidine-3-carboxylate (0.20 mmol, 50.0 mg, 1.0 equiv.) and (*E*)-4,4,5,5-tetramethyl-2-(tridec-1-enyl)-1,3,2-dioxaborolane (0.30 mmol, 90.3 mg, 1.5 equiv.) via pipet. DMF (0.1 mL, 2.0 M) and acetic acid (0.78 mmol, 46.8 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.02 mmol, 9.8 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.22 mmol, 29.4 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 7% ethyl acetate/hexanes as eluent to yield (*S*)-*tert*-butyl 4-((2*E*,4*E*)-hexadeca-2,4-dienoyl)-2,2-dimethyloxazolidine-3-carboxylate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (46.5 mg, 0.11 mmol, 54%); run 2 (45.2 mg, 0.10 mmol, 52%). **Average Yield = 53%.** ^{1}H NMR (400 MHz, C_6D_6) δ major rotamer: 7.32 (dd, *J* = 15.6, 11.2 Hz,

1H), 6.15 (d, *J* = 15.2 Hz, 1H), 5.89 (dd, *J* = 14.8, 11.2 Hz, 1H), 5.73 (dt, *J* = 14.8, 7.2 Hz, 1H), 4.27 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.66 (m, 2H), 1.88 (s, 3H), 1.80 (m, 2H), 1.55 (s, 3H), 1.33 (s, 9H), 1.3-1.0 (m, 18H), 0.84 (t, *J* = 7.2, 3H). minor rotamer: 7.30-7.20 (m, 1H), 6.10 (d, *J* = 15.2 Hz, 1H), 5.90-5.80 (m, 1H), 5.70-5.58 (m, 1H), 4.56 (m, 1H), 3.75 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ major rotamer: 196.6, 152.3, 147.1, 146.5, 144.8, 129.8, 123.8, 96.0, 80.5, 66.6, 65.6, 33.9, 32.9, 30.7, 30.6, 30.4 (2C), 30.1, 29.5, 28.9, 26.2, 25.0, 23.7, 14.9 minor rotamer: 196.1, 152.9, 148.7, 146.0, 144.7, 129.9, 125.0, 95.0, 66.2, 65.4. IR (neat, cm^{-1}) 3011, 2927, 2855, 1710. HRMS (ESI) *m/z* calculated for $C_{26}H_{46}NO_4$ $[M+H]^+$: 436.3427, found 436.3426. $[\alpha]^{27}_D$ = -41.8° (c = 2.5, $CHCl_3$). Spectral data has previously been reported and is in agreement.[18]



(2*E*,4*E*)-7-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added 1-(piperidin-1-yl)prop-2-en-1-one (0.15 mmol, 21.3 mg, 1.0 equiv.) and (*E*)-2-(4-(benzo[*d*][1,3]dioxol-5-yl)but-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.23 mmol, 69.5 mg, 1.5 equiv.) via pipet. DMF (0.08 mL, 2.0 M) and acetic acid (0.61 mmol, 36.7 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.015 mmol, 7.5 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.17 mmol, 23.0 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40°C for 72 hours.

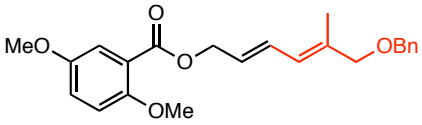
After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 30% ethyl acetate/hexanes as eluent to yield (2*E*,4*E*)-7-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one as a crystalline solid. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (31.1 mg, 0.10 mmol, 65%); run 2 (31.6 mg, 0.10 mmol, 66%). **Average Yield = 66%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 6.24 (d, *J* = 14.8 Hz, 1H), 6.16 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.02 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.90 (s, 2H), 3.58 (br s, 2H), 3.45 (br s, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.39 (apt. q, *J* = 7.6 Hz, 2H), 1.67-1.58 (m, 2H), 1.58-1.48 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 147.8, 145.9, 142.7, 141.1, 135.4, 129.7, 121.4, 119.3, 109.0, 108.4, 101.0, 47.0, 43.4, 35.2, 36.9, 25.8, 24.9. IR (neat, cm^{-1}) 3016, 2995, 2935, 2854, 1651. HRMS (ESI) *m/z* calculated for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1756, found 314.1750. Spectral data has previously been reported and is in agreement.[19]



(*R*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-methoxyocta-2,4-dienyl benzoate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*R*)-*tert*-butyl(3-methoxypent-4-enyloxy)dimethylsilane

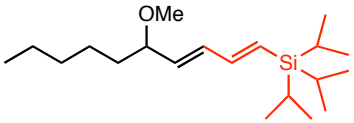
(0.21 mmol, 48.3 mg, 1.0 equiv.) and (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl benzoate (0.42 mmol, 121.0 mg, 2.0 equiv.) via pipet. DMF (0.11 mL, 2.0 M) and acetic acid (0.84 mmol, 50.4 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.02 mmol, 10.5 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.23 mmol, 31.4 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield (*R*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-methoxyocta-2,4-dienyl benzoate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (41.0 mg, 0.11 mmol, 50%); run 2 (41.8 mg, 0.11 mmol, 50%). **Average Yield = 50%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.37 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.20 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.86 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.58 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 2H), 3.76 (apt. q, *J* = 7.6 Hz, 1H), 3.73-3.65 (m, 1H), 3.60 (dt, *J* = 10.0, 6.0 Hz, 1H), 3.24 (s, 3H), 1.82-1.71 (m, 1H), 1.70-1.56 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 135.7, 133.7, 133.2, 131.3, 130.4, 129.8, 128.6, 127.0, 78.7, 65.2, 59.4, 56.6, 38.9, 26.1, 18.5, -5.1, -5.2. IR (neat, cm^{-1}) 3033, 3016, 2953, 2929, 2858, 2819, 1722.

HRMS (ESI) *m/z* calculated for $C_{22}H_{34}O_4SiNa$ $[M+Na]^+$: 413.2124, found 413.2121. Enantiopurity of the product was determined by synthesis of the racemic product followed by HPLC analysis with a Daicel Chemical Industries, LTD chiral OD-H, 0.46 cm x 25 cm column. A flow rate of 1.0 mL/min and 43 psi with 10% *i*-PrOH/hexanes as eluent gave the *R*-isomer at 4.783 min and the *S*-isomer at 5.179 min. Enatiopurtiy was determined to be >99%. $[\alpha]^{24}_D$ = +2.4, c = 1.0, $CHCl_3$. Spectral data has previously been reported and is in agreement.[20]



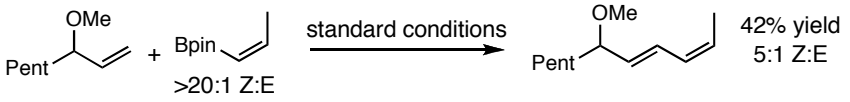
(2*E*,4*E*)-6-(benzyloxy)-5-methylhexa-2,4-dienyl 2,5-dimethoxybenzoate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added allyl 2,5-dimethoxybenzoate (0.23 mmol, 51.1 mg, 1.0 equiv.) and (*E*)-2-(3-(benzyloxy)-2-methylprop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.35 mmol, 99.4 mg, 1.5 equiv.) via pipet. DMF (0.12 mL, 2.0 M) and acetic acid (0.92 mmol, 55.2 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.023 mmol, 11.6 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.25 mmol, 34.4 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After

concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (2*E*,4*E*)-6-(benzyloxy)-5-methylhexa-2,4-dienyl 2,5-dimethoxybenzoate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E*:*Z* 10:1. Run 1 (62.4 mg, 0.16 mmol, 71%); run 2 (63.3 mg, 0.17 mmol, 72%). **Average Yield = 72%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 6H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.94 (d, *J* = 9.5 Hz, 1H), 6.67 (dd, *J* = 15.0, 11.5 Hz, 1H), 6.15 (d, *J* = 11.0 Hz, 1H), 5.90 (dt, *J* = 15.0, 6.5 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 4.00 (s, 2H), 3.89 (s, 3H), 2.82 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 153.7, 153.1, 138.5, 136.5, 130.1, 128.5, 127.8, 127.7, 126.8, 125.7, 120.7, 119.7, 116.1, 114.0, 75.5, 71.9, 65.6, 56.9, 56.0, 14.6. IR (neat, cm^{-1}) 3062, 3030, 2999, 2935, 2914, 2850, 2837, 1728. HRMS (ESI) *m*/*z* calculated for $C_{23}H_{26}O_5Na$ $[M+Na]^+$: 405.1678, found 405.1670. This molecule has previously been reported; however, no spectral data was available.[21]



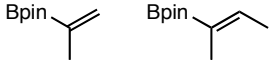
Triisopropyl((1*E*,3*E*)-5-methoxydeca-1,3-dienyl)silane: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added 3-methoxyoct-1-ene (0.28 mmol, 39.8 mg, 1.0 equiv.) and (*E*)-triisopropyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (0.42 mmol, 130.2 mg, 1.5 equiv.) via pipet. DMF (0.14 mL, 2.0 M) and acetic acid (1.12 mmol, 67.2 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.028 mmol, 14.1 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.31 mmol, 41.9 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the

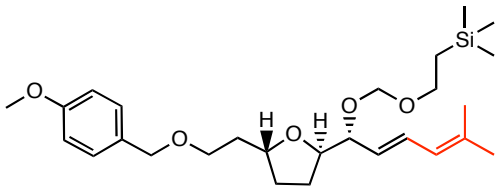
vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 2% ethyl acetate/hexanes as eluent to yield triisopropyl((1*E*,3*E*)-5-methoxydeca-1,3-dienyl)silane as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. 17:1 and *E:Z* >20:1. Run 1 (56.2 mg, 0.17 mmol, 62%); run 2 (56.6 mg, 0.17 mmol, 62%). **Average Yield = 62%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 18.8, 10.0 Hz, 1H), 6.16 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.74 (d, *J* = 18.8 Hz, 1H), 5.49 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.53 (apt. q, *J* = 7.6 Hz, 1H), 3.25 (s, 3H), 1.66-1.52 (m, 1H), 1.52-1.39 (m, 1H), 1.39-1.10 (m, 6H), 1.14-0.94 (m, 21H), 0.86 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 135.9, 134.3, 128.9, 82.3, 56.5, 35.8, 32.1, 25.3, 22.8, 18.9, 14.3, 11.1. IR (neat, cm^{-1}) 2956, 2941, 2891, 2866. HRMS (EI) *m/z* calculated for $C_{20}H_{40}OSi$ $[M]^+$: 324.2849, found 324.2840.



Cis boron coupling partners lost stereochemistry when coupled with the terminal olefin substrate in Table 1 of the manuscript.

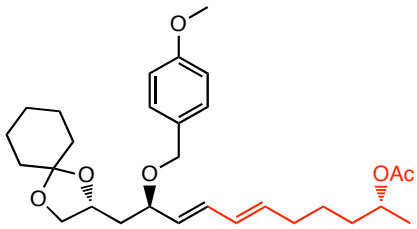
The following boron compounds did not react with the terminal olefin substrate in Table 1 of the manuscript.





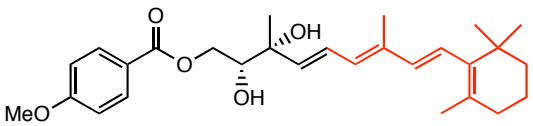
(2-(((*R*,*E*)-1-((2*R*,5*R*)-5-(2-(4-methoxybenzyloxy)ethyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dienyloxy)methoxy)ethyl)trimethylsilane: To a flame dried 2 mL borosilicate vial with a O_2 balloon was added (2-(((*R*)-1-((2*R*,5*R*)-5-(2-(4-methoxybenzyloxy) ethyl)tetrahydrofuran-2-yl)allyloxy)methoxy)ethyl)trimethylsilane (0.10 mmol, 42.2 mg, 1.0 equiv.) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (0.20 mmol, 36.4 mg, 2.0 equiv.) via pipet. DMF (0.05 mL, 2.0 M) and acetic acid (0.40 mmol, 24.0 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.02 mmol, 10.0 mg, 20 mol%) and 2,6-dimethylbenzoquinone (0.11 mmol, 15.0 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with O_2 prior to removing the balloon and sealing the vial with stirring at 50°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) [50 mL] was added. The organics were separated and rinsed once more with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15% ethyl acetate/hexanes as eluent to yield (2-(((*R*,*E*)-1-((2*R*,5*R*)-5-(2-(4-methoxybenzyloxy)ethyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dienyloxy)methoxy)ethyl)trimethylsilane as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E*:*Z* >20:1. Run 1 (32.8 mg, 0.062 mmol, 69%); run 2 (32.4 mg, 0.068 mmol, 68%). **Average Yield = 69%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.47 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.85 (d, *J* = 11.0 Hz, 1H), 5.41 (dd, *J* = 15.0, 7.5 Hz, 1H), 4.76 (d, *J*

= 6.5 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 4.48-4.40 (m, 2H), 4.12-4.00 (m, 3H), 3.82 (s, 3H), 3.82-3.75 (s, 1H), 3.62-3.52 (m, 3H), 2.10-1.84 (m, 3H), 1.80 (s, 3H), 1.78 (s, 3H), 1.78-1.62 (m, 2H), 1.62-1.48 (m, 1H), 0.95 (dt, *J* = 8.5, 1.0 Hz, 2H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 136.5, 131.0, 130.9, 129.4, 126.9, 124.7, 113.9, 92.3, 80.9, 79.3, 77.1, 72.8, 67.8, 65.1, 55.5, 36.0, 32.3, 28.5, 26.2, 18.6, 18.3, -1.2. IR (neat, cm^{-1}) 3041, 3010, 2951, 2916, 2895, 2873, 2860. HRMS (ESI) *m/z* calculated for $C_{27}H_{44}O_5SiNa$ $[M+Na]^+$: 499.2856, found 499.2859. $[\alpha]^{25}_D$ = -56.1, c = 1.0 $CHCl_3$.



(2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl acetate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*R*)-2-((*R*)-2-(4-methoxybenzyloxy)but-3-enyl)-1,4-dioxaspiro[4.5]decane (0.10 mmol, 33.2 mg, 1.0 equiv.) and (*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-yl acetate (0.15 mmol, 42.3 mg, 1.5 equiv.) via pipet. DMF (0.05 mL, 2.0 M) and acetic acid (0.40 mmol, 24.0 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.01 mmol, 5.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.11 mmol, 15.0 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) [50 mL] was added. The organics were separated and rinsed once more with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was

purified via silica chromatography (75 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl acetate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E*:*Z* >20:1. Run 1 (24.8 mg, 0.051 mmol, 51%); run 2 (24.0 mg, 0.051 mmol, 51%). **Average Yield = 51%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.15 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.03 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.67 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.45 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.88 (apt q, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.24 (d, *J* = 11.6 Hz, 1H), 4.25-4.15 (m, 1H), 4.01 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.93 (dt, *J* = 8.4, 4.4 Hz, 1H), 3.78 (s, 3H), 3.48 (t, *J* = 8.0 Hz, 1H), 2.08 (q, *J* = 6.8 Hz, 2H), 2.01 (s, 3H), 1.80-1.72 (m, 2H), 1.64-1.30 (m, 14H), 1.24-1.14 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 159.3, 135.1, 132.8, 131.7, 130.9, 130.0, 129.5, 114.0, 109.1, 73.2, 71.0, 70.2, 69.9, 55.5, 40.7, 36.8, 35.7, 32.6, 25.4, 25.2, 24.2, 24.1, 21.6, 20.2. IR (neat, cm^{-1}) 3012, 2937, 2860, 1736. HRMS (ESI) *m*/*z* calculated for $C_{29}H_{42}O_6Na$ $[M+Na]^+$: 509.2879, found 509.2878. $[\alpha]^{24}_D$ = +32.8, c = 1.0 $CHCl_3$.



(2*R*,3*R*,4*E*,6*E*,8*E*)-2,3-dihydroxy-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-4,6,8-trienyl 4-methoxybenzoate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (2*R*,3*R*)-2,3-dihydroxy-3-methylpent-4-enyl 4-methoxybenzoate (0.14 mmol, 37.2 mg, 1.0 equiv.) and 4,4,5,5-tetramethyl-2-((1*E*,3*E*)-2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl) buta-1,3-dienyl)-1,3,2-dioxaborolane (0.21 mmol, 66.4 mg, 1.5 equiv.) via pipet. DMF (0.07 mL, 2.0 M) and acetic acid (0.56

mmol, 33.6 mg, 4.0 equiv.) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.014 mmol, 7.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.15 mmol, 20.9 mg, 1.1 equiv.) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40ºC for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and N_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 30% ethyl acetate/hexanes as eluent to yield (2*R*,3*R*,4*E*,6*E*,8*E*)-2,3-dihydroxy-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-4,6,8-trienyl 4-methoxybenzoate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (31.8 mg, 0.07 mmol, 51%); run 2 (34.3 mg, 0.08 mmol, 54%). **Average Yield = 53%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.74 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.15 (d, *J* = 16.4 Hz, 1H), 6.03 (d, *J* = 16.4 Hz, 1H), 6.01 (d, *J* = 10.8 Hz, 1H), 5.79 (d, *J* = 15.2 Hz, 1H), 4.48 (dd, *J* = 12.0, 3.2 Hz, 1H), 4.31 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.89-3.83 (m, 1H), 3.83 (s, 3H), 2.74 (br d, *J* = 3.2 Hz, 1H), 2.31 (br s, 1H), 1.98 (t, *J* = 6.4 Hz, 2H), 1.92 (s, 3H), 1.67 (s, 3H), 1.64-1.52 (m, 2H), 1.48-1.39 (m, 2H), 1.38 (s, 3H), 0.99 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 163.8, 138.0, 137.6, 136.9, 136.1, 132.0, 129.5, 128.8, 127.5, 126.6, 122.3, 113.9, 76.3, 74.5, 66.0, 55.7, 39.8, 34.4, 33.2, 29.1, 23.6, 21.9, 19.5, 12.9. IR (neat, cm^{-1}) 3450 (br), 3032, 2956, 2926, 2864, 1712. HRMS (ESI) *m/z* calculated for $C_{28}H_{38}O_5Na$ $[M+Na]^+$: 477.2617, found 477.2607. $[\alpha]^{27}_D$ = +15.2, c =

0.036 MeOH; $[\alpha]^{26}_{D}$ = +11.1, c = 1.0 MeOH. Spectral data has previously been reported and is in agreement.[22]

3.5 REFERENCES

[1] Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 999.

[2] Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466.

[3] (a) Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Ed; Wiley-VCH: New York, 2004. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *ACIE* **2005**, *44*, 4442. (c) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teply, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150. d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474. For examples of carbonyl olefination methods see: (e) Mori, Y.; Asai, M.; Kawade, J.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315. (f) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685. (g) Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1941.

[4] For a reviews of the Heck reaction see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (c) Heck, R. F. *Comprehensive Organic Synthesis;* Trost, B. M., Ed; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.

[5] (a) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 8217. (c) Stang, E. M.; White, M. C. *Nature Chem.* **2009**, *1*, 547.

[6] (a) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (b) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313. (c) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.

[7] (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786. (c) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456. (d) Petasis, N. A.; Releđjian, R.; Sun, Y.-P.; Nagulapalli, K. C.; Tjonahen, E.; Yang, R.; Serhan, C. N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1382. (e) Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron: Asym.* **2005**, *16*, 3107. (f) Kabalka, G. W.; Mereddy, A. R. *Organomet.* **2004**, *23*, 4519.

[8] Zr cat. hydroboration: (a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. Wittig-type olefination: (b) Matterson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230. Vinyl halides or triflates substitution: (c) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001. (f) Uenishi, J.; Matsui, K.; Wada, A. *Tetrahedron Lett.* **2003**, *44*, 3093. For stereodefined trisubstituted boronic esters from alkynes: (d) Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 247. Hydroboration: (e) Pietruszka, J.; Schöne, N.; Frey, W.; Grundl, L. *Chem. Eur. J.* **2008**, *14*, 5178. (g) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482. Rh/Ir cat. hydroboration: (g) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990. Grubbs metathesis: (h) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

[9] (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7. (b) Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 1221. (c) Littke, A.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

[10] Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

[11] (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (b) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270.

[12] (a) Chun, J.; Li, G.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2002**, *67*, 2600. (b) Smith, A. B.; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.

[13] (a) de Araújo-Júnior, J. X.; de M. Duarte, C.; de O. Chaves, M. C.; Parente, J. P.; Fraga, C. A. M.; Barreiro, E. J. *Syn. Comm.* **2001**, *31*, 117. (b) Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213.

[14] Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613.

[15] Yadav, J. S.; Kumar, M. R.; Sabitha, G. *Tetrahedron Lett.* **2008**, *49*, 463.

[16] a) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435. b) Alvarez, S.; Alvarez, R.; de Lera, A. R. *Tetrahedron: Asym.* **2004**, *15*, 839. c) Montenegro, J.; Bergueiro, J.; Saá, C.; López, S. *Org. Lett.* **2009**, *11*, 141. d) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683.

[17] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[18] Chun, J.; Li, G.; Byun, H. –S.; Bittman, R. *J. Org. Chem.* **2002**, *67*, 2600.

[19] Araujo-Junior, J. X. D.; Da-Cunha, E. V. L.; Chaves, M. C. D. O.; Gray, A. I. *Phytochemistry* **1997**, *44*, 559.

[20] Smith, A. B.; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.

[21] Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213.

[22] Alvarez, S.; Alvarez, R.; de Lera, A. R. *Tetrahedron: Assymetry* **2004**, *15*, 839.